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Immunoglobulin for alloimmune hemolytic disease in neonates (Review)

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[Intervention Review]

Immunoglobulin for alloimmune hemolytic disease in neonates

Carolien Zwiers[1], Mirjam EA Scheffer-Rath[2], Enrico Lopriore[2], Masja de Haas[3,4], Helen G Liley[5]

[1]Department of Obstetrics, Leiden University Medical Center, Leiden, Netherlands. [2]Department of Pediatrics, Division of Neonatology, Leiden University Medical Center, Leiden, Netherlands. [3]Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, Netherlands. [4]Immunohematology Diagnostics, Sanquin Diagnostic Services, Amsterdam, Netherlands. [5]Mater Mothers' Hospital, Mater Research, The University of Queensland, South Brisbane, Australia

Contact address: Helen G Liley, Mater Mothers' Hospital, Mater Research, The University of Queensland, South Brisbane, Australia. Helen.Liley@mater.org.au.

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ABSTRACT

Background

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

Objectives

To assess the effect and complications of IVIg in newborn infants with alloimmune HDN on the need for and number of exchange transfusions.

Search methods

We performed electronic searches of CENTRAL, PubMed, Embase (Ovid), Web of Science, CINAHL (EBSCOhost), Academic Search Premier, and the trial registers ClinicalTrials.gov and controlled-trials.com in May 2017. We also searched reference lists of included and excluded trials and relevant reviews for further relevant studies.

Selection criteria

We considered all randomized and quasi-randomized controlled trials of IVIg in the treatment of alloimmune HDN. Trials must have used predefined criteria for the use of IVIg and exchange transfusion therapy to be included.

Data collection and analysis

We used the standard methods of Cochrane and its Neonatal Review Group. We assessed studies for inclusion and two review authors independently assessed quality and extracted data. We discussed any differences of opinion to reach consensus. We contacted investigators for additional or missing information. We calculated risk ratio (RR), risk difference (RD) and number needed to treat for an additional beneficial outcome (NNTB) for categorical outcomes. We calculated mean difference (MD) for continuous variables. We used GRADE criteria to assess the risk of bias for major outcomes and to summarize the level of evidence.

Main results

Nine studies with 658 infants fulfilled the inclusion criteria. Term and preterm infants with Rh or ABO (or both) incompatibility were included. The use of exchange transfusion decreased significantly in the immunoglobulin treated group (typical RR 0.35, 95% CI 0.25 to 0.49; typical RD -0.22, 95% CI -0.27 to -0.16; NNTB 5). The mean number of exchange transfusions per infant was also significantly lower in the immunoglobulin treated group (MD -0.34, 95% CI -0.50 to -0.17). However, sensitivity analysis by risk of bias showed that in the only two studies in which the treatment was masked by use of a placebo and outcome assessment was blinded, the results differed; there was no difference in the need for exchange transfusions (RR 0.98, 95% CI 0.48 to 1.98) or number of exchange transfusions (MD -0.04, 95% CI -0.18 to 0.10). 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 exchange transfusion in infants treated with IVIg, the applicability of the results is limited because of low to very low quality of evidence. Furthermore, the two studies at lowest risk of bias show no benefit of IVIg in reducing the need for and number of exchange transfusions. Based on these results, we have insufficient confidence in the effect estimate for benefit of IVIg to make even a weak recommendation for the use of IVIg for the treatment of alloimmune HDN. Further studies are needed before the use of IVIg for the treatment of alloimmune HDN can be recommended, and should include blinding of the intervention by use of a placebo as well as sufficient sample size to assess the potential for serious adverse effects.

PLAIN LANGUAGE SUMMARY

Immunoglobulin for alloimmune hemolytic disease in newborns

Review question

Is IVIg effective in reducing the need for exchange transfusion in newborns with alloimmune hemolytic disease of the newborn (HDN)?

Background

In alloimmune HDN, maternal antibodies (circulating proteins that are produced by the immune system in response to the presence of a foreign substance) are produced against fetal blood cells. These antibodies are transferred across the placenta and destroy red blood cells, leading to fetal anemia (deficiency of red cells in the unborn baby). Intrauterine (within the womb) blood transfusion is used to treat severe fetal anemia. After birth, the antibodies persist in the infant and cause hyperbilirubinemia (a raised blood level of an orange-yellow pigment (bilirubin, a waste product of a degrading red blood cell) with the risk of serious brain damage (kernicterus) and anemia. Traditional treatment of hyperbilirubinemia consists of (intensive) phototherapy (light treatment) and exchange transfusion (where the baby's blood is replaced with that of a donor; ET). Because ET is an invasive, high risk procedure, alternative treatments such as intravenous immunoglobulin (IVIg), have been investigated. IVIg is thought to reduce the rate of hemolysis and consequently the need for ETs.

Study characteristics

We searched the medical literature to 19 May 2017 and found nine randomized (clinical studies where people are randomly put into one of two or more treatment groups) or partly (quasi) randomized trials (including 658 participants) that assessed the efficiency of IVIg in infants with alloimmune HDN.

Key results

Analysis of all included studies showed a reduction in the need for and number of ETs in infants treated with IVIg combined with phototherapy compared to infants treated with phototherapy only. However, this was not confirmed in an analysis of the two placebo-controlled studies (where a pretend treatment was given). There was no difference in the need for or number of top-up transfusions.

Quality of evidence

The evidence from the studies was very low quality. However, two studies used a placebo, thereby minimizing bias and allowing blinding of the researchers assessing the response. These studies were consistent with each other and yielded moderate quality evidence (with

a relatively small total number of participants involved (172) being the only reason to not regard the level of evidence from them as high) that IVIg was ineffective in preventing ET or top-up transfusions.

Conclusion

Based on all included studies, we could make no conclusions on the benefit of IVIg in preventing ET or top-up transfusion. However, the two placebo-controlled trials provided evidence of moderate quality that IVIg was ineffective in preventing ET or top-up transfusion, and therefore routine use in alloimmune HDN should not be recommended. However, since there was some evidence that IVIg reduced hemolysis (in laboratory studies), future high-quality studies are needed to determine whether IVIg has limited role in some infants with alloimmune HDN.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Intravenous immunoglobulin plus phototherapy compared to phototherapy alone for alloimmune hemolytic disease in neonates

Patient or population: neonates with alloimmune hemolytic disease
Settings: -
Intervention: IVIg + phototherapy
Comparison: phototherapy

Outcomes	№ of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with phototherapy alone	Risk difference with IVIg + phototherapy
Use of ET (≥ 1); all studies	658 (9 RCTs)	⊕◯◯◯ **Very low**[1,2,3]	**RR 0.35** (0.25 to 0.49)	Study population	
				329 per 1000	214 fewer per 1000 (247 fewer to 168 fewer)
Use of ET (≥ 1); placebo-controlled studies	172 (2 RCTs)	⊕⊕⊕◯ **Moderate**[4]	**RR 0.98** (0.48 to 1.98)	Study population	
				153 per 1000	3 fewer per 1000 (80 fewer to 150 more)
ETs performed per infant; all studies	658 (9 RCTs)	⊕◯◯◯ **Very low**[1,2,3,5]	-	The mean ETs per infant for all studies was 0	MD 0.34 lower (0.5 lower to 0.17 lower)
ETs performed per infant; placebo-controlled studies	172 (2 RCTs)	⊕⊕⊕◯ **Moderate**[4,5]	-	The mean ETs per infant for placebo-controlled studies was 0	MD 0.04 lower (0.18 lower to 0.1 higher)
Use of top-up transfusion in 1st week of life; all studies	378 (4 RCTs)	⊕⊕◯◯ **Low**[6,7]	**RR 1.05** (0.65 to 1.69)	Study population	
				130 per 1000	6 more per 1000 (45 fewer to 89 more)

Use of top-up transfusion after 1st week of life; all studies	507 (7 RCTs)	⊕◯◯◯ **Very low**[1,8,9]	**RR 1.16** (0.97 to 1.38)	Study population	
				219 per 1000	35 more per 1000 (7 fewer to 83 more)
Maximum total serum bilirubin (μmol/L); all studies	451 (6 RCTs)	⊕◯◯◯ **Very low**[10,11,12]	-	The mean maximum serum bilirubin (μmol/L) for all studies was 0	MD 25.39 lower (34.07 lower to 16.7 lower)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **ET:** exchange transfusion; **IVIg:** intravenous immunoglobulin; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality**:** we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality**:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality**:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality**:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]In three studies, the method of randomization was not stated and there was inadequate concealment of random sequence (selection bias). In seven studies, there was no blinding of personnel (performance bias) and in five studies, no blinding of outcome assessment (detection bias). Among other potential sources of bias were that mean bilirubin levels at study entry were already higher than the threshold for the outcome (ET) in one study, differences between study groups despite randomization (one study), postrandomization withdrawals or cross-over between study groups (two studies) and criteria for ET differing between treatment arms (one study).
[2]Substantial heterogeneity: $Chi^2 = 34.63$, df = 8 (P = 0.0003), $I^2 = 77\%$.
[3]Four studies did not clearly specify use of intensive phototherapy (which should be a routine intervention for infants at high risk of ET).
[4]Total number of participants in these two trials was low, increasing the risk of possible bias.
[5]Only a few infants needed a second ET.
[6]In one trial, the methods of randomization and allocation concealment were not stated. In two studies, there was no blinding of personnel (performance bias).
[7]Combined studies were underpowered for use of top-up transfusion in 1st week. A total of 378 infants were enrolled in all four trials, and the overall frequency of top-up transfusion was low (13.8%).
[8]Substantial heterogeneity: $Chi^2 = 15.60$, df = 5 (P = 0.008); $I^2 = 68\%$.
[9]Due to small differences between treatment groups, the combined studies were underpowered for use of top-up transfusion after 1st week.
[10]Four studies used no method of blinding the intervention.

[11]Substantial heterogeneity: $Chi^2 = 14.82$, df = 5 (P = 0.01); $I^2 = 66\%$.

[12]Peak serum bilirubin in the control group varied 1.86-fold between studies; there was considerably greater variation between studies than between groups within studies.

BACKGROUND

Description of the condition

The use of anti-D immunoglobulin prophylaxis in D-negative women has led to a marked decline in Rh hemolytic disease of the newborn (HDN) (Urbaniak 2000). Sensitization can occur despite immunoprophylaxis, particularly if it is given too late or in insufficient dose. A proportion of HDN is caused by antibodies to antigens other than D and is, therefore, not preventable with anti-D immunoglobulin. Fetal therapy has significantly improved outcome in Rh sensitized fetuses, but it does not comprehensively prevent need for neonatal treatment (van Kamp 2004). 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% to 40% of neonates admitted for Rh or ABO HDN require at least one ET (Steiner 2007; Smits-Wintjens 2011).

The safety of ET has been reported for over 50 years. Published mortality rates vary from 0.53% to 4.7% per infant (Boggs 1960; Panagopoulos 1969; Keenan 1985; Guaran 1992; Jackson 1997; Patra 2004; Badiee 2007). ET-related death is more common in sick or premature infants than in healthy term infants (Boggs 1960; Keenan 1985; Jackson 1997; Steiner 2007). Risks related to ET include adverse cardiorespiratory 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. In the last two decades, ET-related risks have been reported to be as high as 74%, although the incidence of severe adverse events is approximately 3-10% (Ip 2004; Patra 2004; Badiee 2007; Steiner 2007). Because improved perinatal care has reduced the need for ET, the complication rate could increase as clinicians become less experienced with the procedure (Steiner 2007). However, Steiner 2007 reported that over a 21-year period, despite a sharp decline in the number of ETs performed, there was no increase in morbidity and mortality.

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 E-incompatibility with IVIg was published (Hara 1987). Subsequent case reports and case series reported success of IVIg treatment in neonates with both Rh or ABO incompatibility (Kubo 1991; Sato 1991; Ergaz 1993). However, Hammerman 1996a found a reduced or no response to IVIg treatment in infants with ABO incompatibility who had early and severe hemolysis. Since the early 1990s, several quasi-randomized or randomized controlled trials on the use of IVIg (including variations on timing of administration and dose) to reduce ET have been published (Alpay 1999; Dağ oğ lu 1995; Elalfy 2011; Miqdad 2004; Nasseri 2006; Rübo 1992; Santos 2013; Smits-Wintjens 2011; Tanyer 2001; Atici 1996; Garcia 2004; Girish 2008; Hematyar 2011; Huang 2006; Liu 2016; Pishva 2000; Rübo 1996; Spinelli 2001; Voto 1995; Wang 2002).

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 while 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 (INIS Collaborative Group 2011). It is a well-established therapy for alloimmune thrombocytopenia due to maternal and fetal human platelet antigen incompatibility (Winkelhorst 2017). The risk of transmission of viral infection is extremely low (Fischer 1988). Hemolysis and acute renal failure are uncommon complications of IVIg treatment (Copelan 1986). One study showed an increased incidence of sepsis in premature infants receiving prophylactic IVIg (Magny 1991). Since about 2010, several cases of necrotizing enterocolitis in infants with HDN treated with IVIg have been reported (Figueras-Aloy 2010; Corvaglia 2012; Yang 2016+

). Other rare serious adverse effects of IVIg have been described in pediatric and adult cohorts, but not in newborns (Kumar 2006).

How the intervention might work

IVIg might reduce the rate of hemolysis in alloimmune HDN by nonspecific blockade of Fc-receptors on the macrophages that are thought to mediate the destruction of antibody-coated red cells (Urbaniak 1979). Ergaz 1995 demonstrated a decline in carboxyhemoglobin levels in four of five infants treated with IVIg for alloimmune HDN. Hammerman 1996b demonstrated a significant reduction in carboxyhemoglobin levels in 19 of 26 Coombs-positive infants treated with IVIg. Carboxyhemoglobin levels are a sensitive index of hemolysis and hence these studies suggest that immunoglobulin could decrease hemolysis. IVIg is typically formulated in 6% to 12% solutions, so at doses of 0.5 g/kg to 1 g/kg the volume administered is 4 mL/kg to 16 mL/kg. It is possible that this is a sufficient fluid bolus to reduce bilirubin levels modestly through dilution, temporarily slowing their rate of rise and allowing more time for intensive phototherapy to have effect.

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 at low risk of bias. Nevertheless, American Academy of Pediatrics (AAP) guidelines recommend the administration of 0.5 g/kg to 1 g/kg IVIg in alloimmune HDN if total serum bilirubin (TSB) is rising despite intensive phototherapy or if TSB level is within 34 µmol/L to 51 µmol/L (2 mg/dL to 3 mg/dL) of exchange level (AAP 2004). 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 confirmed benefit.

OBJECTIVES

To assess the effect and complications of IVIg in newborn infants with alloimmune HDN on the need for and number of exchange transfusions.

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 other red cell antigens) 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'). Phototherapy, which is widely regarded as a safe and effective standard treatment may have been used in both IVIG and control groups. Early and late IVIg administration were defined (for this review) as IVIg started within (early) or after (late) the first 12 hours of life. Studies must have included 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 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 (statement of adverse events from individual trials only).

Search methods for identification of studies

Electronic searches

We performed electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), PubMed, Embase (Ovid), Web of Science, CINAHL (EBSCOhost), Emcare 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 19 May 2017. The bibliographic databases yielded 1565 references in total of which titles and abstracts were screened. The complete search strategy is attached in the appendix "Complete Search Strategy." In addition to database searches, we searched the trial registers ClinicalTrials.gov and controlled-trials.com. We applied no language restrictions.

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

We used the standard method of Cochrane and its Neonatal Review Group.

Selection of studies

Two review authors independently screened the titles and abstracts of all references for possible inclusion using predefined criteria for inclusion (see below). We obtained a full-text version of the article if a report appeared to meet inclusion criteria for the review, or if it was not clear based on title and abstract. We resolved any disagreements through discussion with other review authors.
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 neonates 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 or at least one of the secondary outcomes (see below) (or both) 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. We resolved any disagreements through discussion and if necessary with the help of a third review author 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. One review author entered data into Review Manager 5 (RevMan 2011; RevMan 2014), and at least one review author checked them.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of included studies using the 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). 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 review author until consensus was reached. For selective reporting, we used the following criteria 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

We calculated the risk ratio (RR) and risk difference (RD) for categorical outcomes, such as the incidence of ET. We calculated the mean difference (MD) for continuous variables, such as the maximum bilirubin level. We also calculated the number needed to treat for an additional beneficial outcome (NNTB) to avoid ET, where the assumed control risk was derived from the mean baseline risk from the studies (Schünemann 2013). We presented 95% confidence intervals (CI).

Dealing with missing data

We contacted investigators for missing information about study design, results or both.

Assessment of heterogeneity

We assessed clinical heterogeneity by determining whether clinical characteristics of participants, interventions, outcome measures and timing of outcome measurements were similar for included studies. We assessed statistical heterogeneity using Chi^2 and I^2 tests. An I^2 statistic of 50% or greater was considered as substantial or considerable heterogeneity according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

We contacted investigators to request missing outcome data when selective reporting bias was suspected based on the criteria described under Assessment of risk of bias in included studies.
If the data remained unavailable and the absence was thought to introduce serious bias, the study was excluded.

Data synthesis

We used Review Manager 5 to synthesize the available data (RevMan 2014). Whether we used a fixed-effect model or a random-effects model depended on the level of clinical heterogeneity and the results of the Chi^2 test and I^2 statistic for heterogeneity (Higgins 2011). If there was substantial heterogeneity, we used a random-effects model was used and examined the sources of heterogeneity. If there was no substantial statistical heterogeneity, we used a fixed-effect model.

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes:

- use of ET (proportion of infants receiving one or more ETs; assessment for all studies and separately for placebo-controlled studies;
- ETs per infant; assessment for all studies and separately for placebo-controlled studies;
- use of top-up transfusion(s) in first week of life (% of infants); all studies;
- use of top-up transfusion(s) after first week of life (% of infants); all studies;
- maximum serum bilirubin; all studies.

Two review authors independently assessed the quality of the evidence for each of the outcomes. We considered evidence from randomized controlled trials as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We used the GRADEpro Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence (GRADEpro GDT).
The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted to determine if effects depend on:

- population:
  - Rh incompatibility;
  - gestational age at birth (less than 37 weeks and 37 weeks or greater);
- intervention:
  - early administration of IVIg: start of IVIg 12 hours or less after birth;
  - late administration of IVIg: start of IVIg more than 12 hours after birth;
  - single versus multiple doses.

As in contemporary care intensive phototherapy is standard care for ABO incompatibility and therefore ETs hardly ever occur in this subgroup nowadays, no subgroup analysis was performed for ABO incompatibility only.

Sensitivity analysis

We conducted a sensitivity analysis based on whether or not the included studies used a placebo and treatment blinding (which had potential to reduce performance bias and detection bias). The two studies that used a placebo were also at low risk of other forms of bias in that they used random sequence generation, allocation concealment, reported complete outcome data for all prespecified outcomes and did not have other apparent risks of bias.

RESULTS

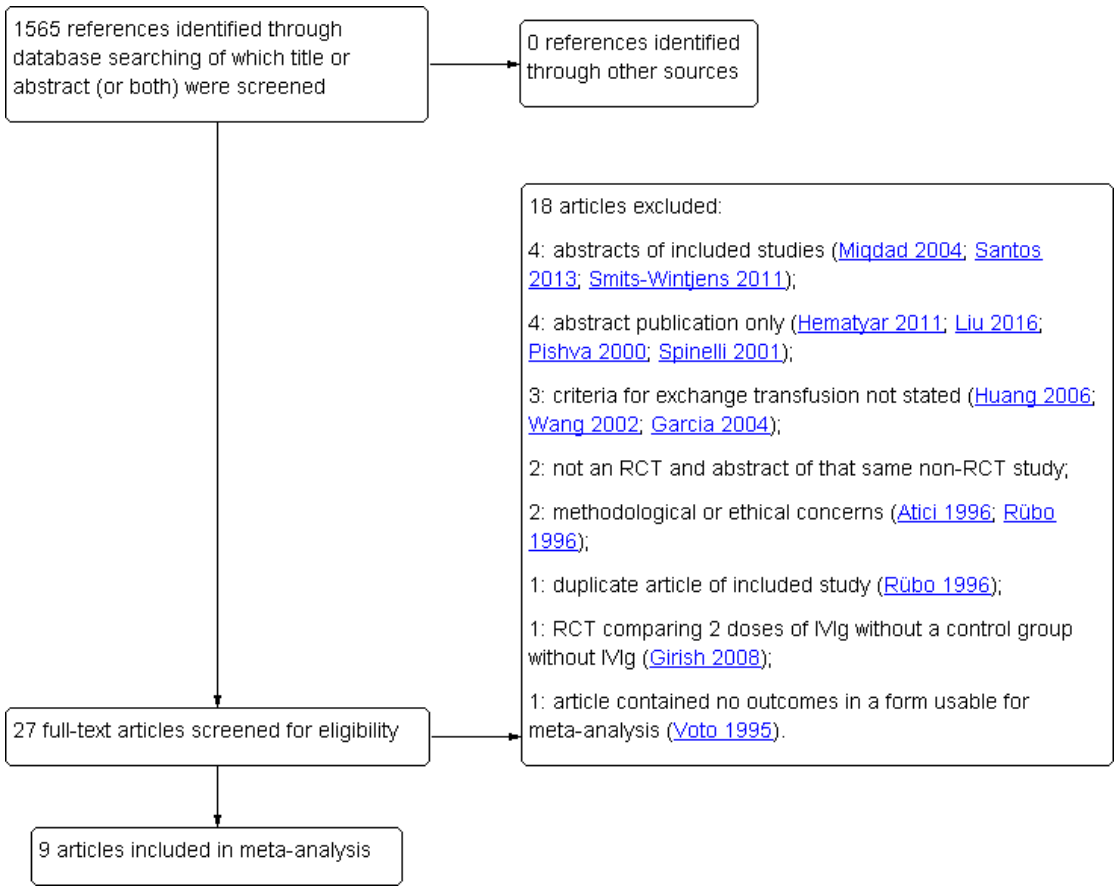
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; and Characteristics of studies awaiting classification tables.

Results of the search

The search conducted up to 19 May 2017 identified 1565 references (see: Appendix 1). After title and abstract screening, the full text of 27 references was screened. After full text screening, nine studies were included in the meta-analysis (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Tanyer 2001; Miqdad 2004; Nasseri 2006; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). Details of the studies are given in the Characteristics of included studies table. Eleven studies were permanently excluded from this review. Details of these studies are given in the Characteristics of excluded studies table. We found no additional studies searching reference lists of included and excluded studies and relevant reviews. A flow diagram of the study selection process is presented in Figure 1. No additional studies were included after an additional search for ongoing studies in the trial registers ClinicalTrials.gov and controlled-trials.com.

Figure 1. Flow diagram of study selection process. IVIg: intravenous immunoglobulin; RCT: randomized controlled trial.



Included studies

The review included nine randomized controlled trials published between 1992 and 2013.

Participants

The nine studies included 658 participants. Five studies included only infants with Rh incompatibility (Rübo 1992; Dağ oğ lu 1995; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). One study included only infants with ABO incompatibility (Miqdad 2004). Two 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, seven both; Nasseri 2006: 21 ABO, 13 Rh). Tanyer 2001 included 34 infants with ABO incompatibility, 18 with Rh incompatibility, two with "subgroup" incompatibility and seven with "more than one incompatibilities." Only Nasseri 2006 reported results for each type of incompatibility separately and Alpay 1999 provided this information through correspondence. Four studies enrolled only term infants of 37 weeks of gestation or greater (Alpay 1999; Tanyer 2001; Nasseri 2006; Elalfy 2011). None of the studies only included premature infants of less than 37 weeks of gestation. Rübo 1992 did not describe details of the gestational age at birth of enrolled infants. Santos 2013 and Smits-Wintjens 2011 provided outcomes for term and preterm infants separately.

Interventions

Seven of nine studies that met the inclusion criteria examined the effect of a single dose of IVIg in combination with phototherapy (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Miqdad 2004; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). One study examined multiple doses (Nasseri 2006), and one study compared groups treated with a single dose or multiple doses with a control group (Tanyer 2001), but was inconsistent in describing which group received a single dose or multiple doses of IVIg and therefore this study was excluded from the (planned) subgroup analysis of single and multiple doses. Two studies used a placebo in addition to phototherapy for the control groups (Smits-Wintjens 2011; Santos 2013). The intensity and topography of phototherapy fits the definition of intensive phototherapy in only three studies (Elalfy 2011; Smits-Wintjens 2011; Santos 2013). Tanyer 2001 used an obsolete model with three overhead lights from a single angle and Miqdad 2004 did not use a phototherapy blanket beneath the baby. 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. Five studies started IVIg 12 hours or less after birth (Rübo 1992; Dağ oğ lu 1995; Elalfy 2011; Smits-Wintjens 2011; Santos 2013), and three studies started IVIg more than 12 hours after birth (Alpay 1999; Tanyer 2001; Nasseri 2006). Miqdad 2004 started IVIg within 12 hours in nine neonates and more than 12 hours in 47 neonates, but they did not report outcomes for early and late IVIg administration separately.

Since phototherapy was used in both treatment and control groups in all studies and is now considered standard of care in HDN, this review is effectively an analysis of the effectiveness of IVIg plus phototherapy versus phototherapy alone.

Outcomes

All included studies reported ET as the primary outcome. Six studies reported mean (or median) number of ETs per infant (Nasseri 2006; Smits-Wintjens 2011) or supplied enough data to calculate these (Rübo 1992; Dağ oğ lu 1995; Tanyer 2001; Elalfy 2011). The authors of four studies provided unpublished data (standard deviation or mean, or both) for ET (Alpay 1999; Miqdad 2004; Smits-Wintjens 2011; Santos 2013). Four studies reported the maximum bilirubin level (Rübo 1992; Dağ oğ lu 1995; Smits-Wintjens 2011; Santos 2013). Two studies provided unpublished data on maximum bilirubin levels (Alpay 1999; Elalfy 2011). Although all studies commented on the duration of phototherapy in their results, only seven studies reported or subsequently provided the numerical data (Alpay 1999; Tanyer 2001; Miqdad 2004; Nasseri 2006; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). These studies all used predefined criteria for commencing phototherapy but not all for ceasing it. Six studies reported or subsequently provided numerical data on the duration of hospitalization (Alpay 1999; Miqdad 2004; Nasseri 2006; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). Only two studies reported (after correspondence) predefined criteria for hospital discharge (Miqdad 2004; Santos 2013). Six studies included top-up transfusion as an outcome (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Miqdad 2004; Nasseri 2006; Smits-Wintjens 2011). Three studies provided additional data on top-up transfusions (Elalfy 2011; Smits-Wintjens 2011; Santos 2013). Smits-Wintjens 2011 did not report top-up transfusions separately for the first week and after the first week of life, but subsequently provided this information. Elalfy 2011 had a follow-up period of only one week after discharge. Three studies reported predefined criteria for top-up transfusions (Alpay 1999; Nasseri 2006; Smits-Wintjens 2011), and one study later provided data through correspondence (Santos 2013). All studies reported short-term adverse events. None of the included studies reported data on neurodevelopmental outcomes. Two studies provided additional information on neurodevelopmental outcomes (Miqdad 2004; Santos 2013).

Excluded studies

We excluded 11 studies. One study only compared groups with a high or a low dose of IVIg (Girish 2008), and four studies were only reported in abstract form and our request for additional information was not (sufficiently) answered (Pishva 2000; Spinelli 2001; Hematyar 2011; Liu 2016). Three studies did not report predefined criteria for the primary outcome ET (Wang 2002; Garcia 2004; Huang 2006). One study did not report any outcome in a usable form for meta-analysis (Voto 1995). Two studies were excluded due to methodological or ethical (or both) concerns (Atici 1996; Rübo 1996). Details of excluded studies are given in the Characteristics of excluded studies table.

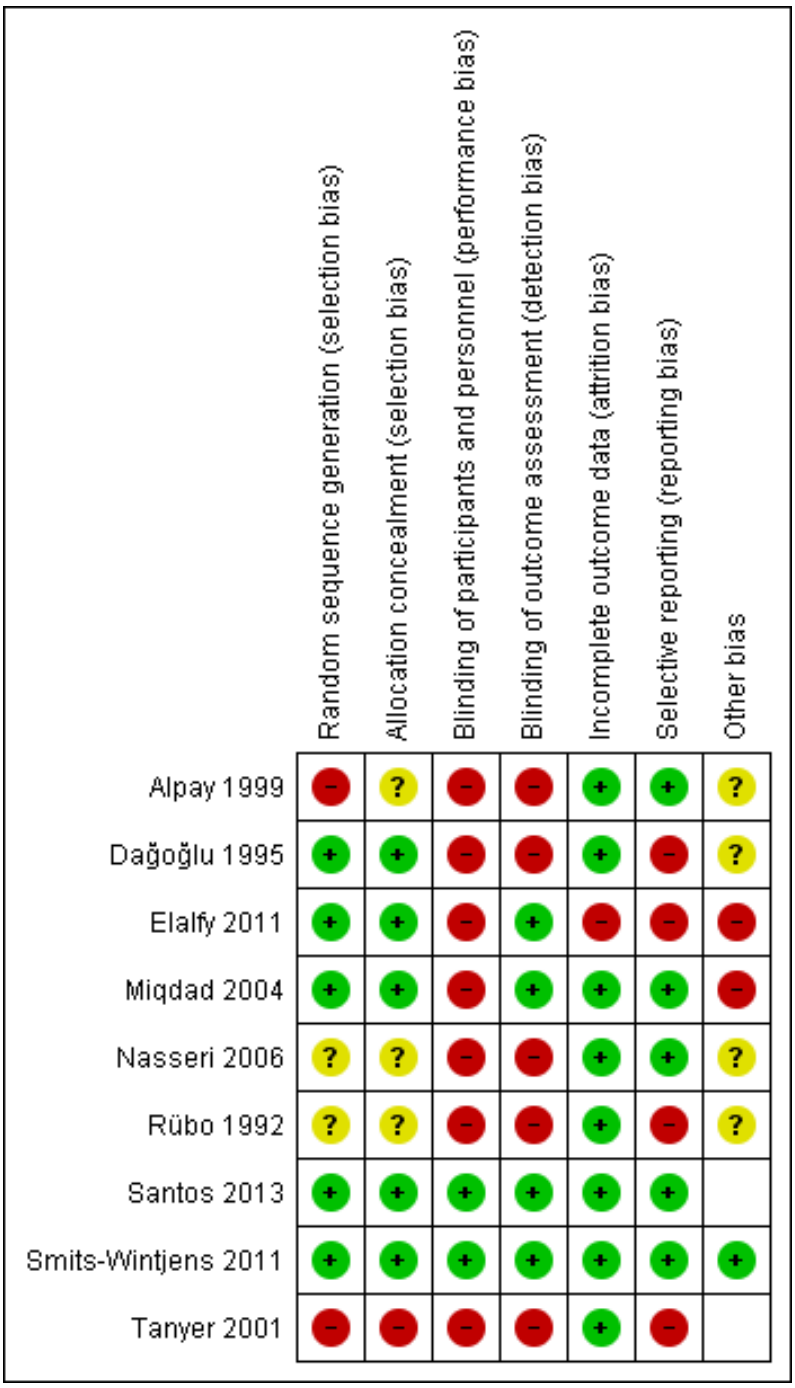
Additional data

We attempted to contact the authors of all studies (except for the six studies that were identified for the previous review (Rübo 1992; Dağ oğ lu 1995; Voto 1995; Alpay 1999; Spinelli 2001; Tanyer 2001) to request further methodological information and results. We successfully contacted the authors of 11 papers (Rübo 1992; Rübo 1996; Alpay 1999; Miqdad 2004; Huang 2006; Elalfy 2011; Hematyar 2011; Smits-Wintjens 2011; Santos 2013) (including contact for the previous review)) in order to obtain additional data or to assist with the determination to include or exclude the study.

Risk of bias in included studies

For details of risk of bias of included studies, see the Characteristics of included studies table and Figure 2.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Allocation

Only five studies reported an adequate method of randomization (Dağ oğ lu 1995; Miqdad 2004; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). Miqdad 2004 and Elalfy 2011 provided information on randomization method only through correspondence. One quasi-randomized controlled trial allocated participants by order of admission (Tanyer 2001). This study was rated as high risk of bias for both random sequence generation and allocation concealment. Alpay 1999 did not state what method of randomisation was used either in the paper or in response to a query from the review authors, commenting only that that the group allocation was decided by attending neonatologists who differed from those who were conducting the study, which we construed to mean that the allocation was not random, and that the allocation was at high risk of bias. Nasseri 2006 and Rübo 1992 stated that babies were randomly assigned to treatment groups but did not provide any detail about the method used and the allocation was therefore considered at unclear risk of bias.

Blinding

Only two studies used a placebo in the control group (Smits-Wintjens 2011; Santos 2013), and were therefore rated as low risk for performance bias and detection bias. After correspondence with the authors of two additional studies, the risk of detection bias was rated as low; Miqdad 2004 explained that data were kept and entered to their database by personnel who were not involved in the management of the cases and Elalfy 2011 explained that the person who performed the randomization was different from the one who conducted the study and the one who analyzed the data. None of the other studies described any method of blinding of intervention after allocation and, therefore, they were rated as high risk of bias on both items.

Incomplete outcome data

Reporting of outcome data was at low risk of bias in seven studies (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Tanyer 2001; Miqdad 2004; Nasseri 2006; Smits-Wintjens 2011; Santos 2013). For six of these studies, there were no missing data. In Rübo 1992, the amount of and reasons for missing data were similar between groups (low risk). One study was at high risk of bias because of a substantial amount of missing data on bilirubin levels (Elalfy 2011).

Selective reporting

Reporting bias was suspected in four studies because important outcomes were either not reported or were not reported in a form that was useable for meta-analysis, or that allowed judgment about local treatment practices (e.g. if the authors only stated that there was no significant difference between groups) (Rübo 1992; Dağ oğ lu 1995; Tanyer 2001; Elalfy 2011). The remaining studies were at low risk of bias.

Other potential sources of bias

Elalfy 2011 had non-random cross-over after randomization and another study used an additional criterion for ET in the control group only (Miqdad 2004). These two studies were at high risk of bias. Dağ oğ lu 1995 used post-randomization consent and although follow-up was complete for all infants for whom consent was obtained, four infants (two randomized to each arm of the study) were excluded because consent was withheld. Two infants were also excluded post-randomization in one other study because of "protocol violations" but no details were given (Rübo 1992). The latter two studies were rated at unclear risk of bias because the review authors were unable to assess the impact of these withdrawals on overall outcomes. Three other studies were rated as unclear risk of bias (Alpay 1999; Nasseri 2006), or low risk of bias (Smits-Wintjens 2011) for a potential risk of bias. For details see 'Risk of bias' tables.

Effects of interventions

See: **Summary of findings for the main comparison** Intravenous immunoglobulin plus phototherapy compared to phototherapy alone for alloimmune hemolytic disease in neonates

Intravenous immunoglobulin plus phototherapy versus control (phototherapy only)

Primary outcomes

Exchange transfusion

The results of nine included studies could be entered into the meta-analysis (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Tanyer 2001; Miqdad 2004; Nasseri 2006; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). Most studies found a statistically significant reduction in the use of ET for IVIg treated infants (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Tanyer 2001; Miqdad 2004; Nasseri 2006; Elalfy 2011). Two studies concluded that the use of (one or more) ETs was not reduced despite using early IVIg in combination with phototherapy (Smits-Wintjens 2011; Santos 2013). The meta-analysis of all nine studies (658 participants) showed that IVIg reduced the need for an ET (typical RR 0.35, 95% CI 0.25 to 0.49; typical RD -0.22, 95% CI -0.27 to -0.16; NNTB 5)

(Analysis 1.1). However, overall, we rated this as very low quality evidence, because, although it was derived from randomized trials, there was very serious risk of bias in most trials, and moderate heterogeneity and serious indirectness, related to the fact that some trials did not use intensive phototherapy, which would be considered standard practice.

Subgroup analysis of infants with only Rh incompatibility supported a reduction in the use of ET with IVIg treatment (371 participants, typical RR 0.38, 95% CI 0.25 to 0.58; NNTB 5) (Analysis 2.1) (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Nasseri 2006; Elalfy 2011; Smits-Wintjens 2011; Santos 2013).

In only those infants born at 37 weeks of gestation or greater, IVIg reduced the use of ETs (391 participants, typical RR 0.39, 95% CI 0.25 to 0.61; NNTB 6) (Analysis 6.1) (Alpay 1999; Tanyer 2001; Nasseri 2006; Elalfy 2011; Santos 2013; Smits-Wintjens 2011). In the subgroup of infants born at less than 37 weeks of gestation, IVIg did not reduce the use of ETs (82 participants, typical RR 0.77, 95% CI 0.31 to 1.91; NNTB 20) (data not shown) (Smits-Wintjens 2011; Santos 2013).

Five studies found reductions in the use of ET where IVIg was used 12 hours or less after birth (335 participants, typical RR 0.41, 95% CI 0.26 to 0.66; NNTB 6) (Analysis 3.1) (Rübo 1992; Dağ oğ lu 1995; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). Reductions were also found in the three studies which used IVIg more than 12 hours after birth (211 participants, typical RR 0.31, 95% CI 0.18 to 0.53; NNTB 4) (data not shown) (Alpay 1999; Tanyer 2001; Nasseri 2006). Subgroup analyses of infants receiving a single dose of IVIg and infants receiving multiples doses of IVIg supported a reduction in the use of ET with IVIg treatment, although there was insufficient evidence to support a dose-response effect (single dose of IVIg: 563 participants, typical RR 0.37, 95% CI 0.26 to 0.53; NNTB 6; Analysis 4.1 (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Miqdad 2004; Elalfy 2011; Smits-Wintjens 2011; Santos 2013); multiple doses of IVIg: 34 participants, RR 0.27, 95% CI 0.09 to 0.81; NNTB 1; Analysis 5.1 (Nasseri 2006)).

However, despite these apparently promising results, analysis of the only two placebo-controlled studies at low risk of all forms of bias showed no reduction in the use of ET (172 participants, typical RR 0.98, 95% CI 0.48 to 1.98) (Analysis 1.1.2) (Smits-Wintjens 2011; Santos 2013). Furthermore, when all studies were considered, heterogeneity was moderate for use of ET (Chi^2 = 11.32, degrees of freedom (df) = 8 (P = 0.18); I^2 = 29%) and was high for ETs per infant (Tau^2 = 0.04; Chi^2 = 36.77, df = 8 (P < 0.0001); I^2 = 78%), whereas the results of both these outcomes for the placebo-controlled trials were highly consistent (I^2 = 0% for both). We rated the quality of evidence from the two placebo-controlled studies as moderate, downgrading it only for imprecision because of the low total number of participants.

Overall, immunoglobulin treatment also led to a reduction in the mean number of ETs per infant (658 participants, MD -0.34, 95% CI -0.50 to -0.17). We assessed the level of evidence from the whole group of studies as very low, again downgrading the evidence from randomized trials because of very serious risk of bias, high heterogeneity, indirectness and imprecision. In contrast, analysis of the two placebo-controlled studies were consistent with each other and when considered alone, yielded moderate quality of evidence that IVIg did not reduce the number of ETs (172 participants, MD -0.04, 95% CI -0.18 to 0.10) (Analysis 1.2.2).

Secondary outcomes

Top-up transfusions during and after the first week

The results of four studies could be entered in the meta-analysis of the use of top-up transfusions in the first week of life (Alpay 1999; Elalfy 2011; Smits-Wintjens 2011; Santos 2013) and of seven studies for the use of top-up transfusions after the first week of life (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Miqdad 2004; Nasseri 2006; Smits-Wintjens 2011; Santos 2013). IVIg did not increase the need for top-up transfusions during the first week (378 participants, typical RR 1.05, 95% CI 0.65 to 1.69) (Analysis 1.3) or in the period after the first week (507 participants, typical RR 1.16, 95% CI 0.97 to 1.38) (Analysis 1.5). 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 (first week: typical RR 1.08, 95% CI 0.65 to 1.77 (Analysis 2.3); after first week: typical RR 1.09, 95% CI 0.92 to 1.28 (Analysis 2.5)); infants born 37 weeks or more of gestation (first week: typical RR 0.91, 95% CI 0.48 to 1.74 (Analysis 6.3); after first week: typical RR 1.18, 95% CI 0.81 to 1.71 (Analysis 6.5)); infants born less than 37 weeks of gestation (first week: typical RR 1.39, 95% CI 0.70 to 2.73; after first week: typical RR 1.24, 95% CI 0.93 to 1.67 (data not shown)); infants treated with IVIg 12 hours or less after birth (first week: typical RR 1.18, 95% CI 0.70 to 2.00 (Analysis 3.3); after first week: typical RR 1.04, 95% CI 0.89 to 1.22 (Analysis 3.5)); and in infants treated with a single dose of IVIg (first week: typical RR 1.05, 95% CI 0.65 to 1.69 (Analysis 4.3); after first week: typical RR 1.13, 95% CI 0.95 to 1.33 (Analysis 4.5)). Although the need for top-up transfusions during the first week of life was not increased for the subgroup of infants treated with IVIg more than 12 hours after birth (typical RR 0.71, 95% CI 0.24 to 2.12) (data not shown), the need for top-up transfusions after the first week of life was increased with late IVIg treatment (typical RR 8.00, 95% CI 1.03 to 62.26) (data not shown). However, the CIs were very large and the lower CI limit was nearly one. For infants treated with multiple IVIg doses, the use of top-up transfusions after the first week of life was not increased (typical RR 5.65, 95% CI 0.25 to 126.87) (Analysis 5.3) and not estimable for the first week of life.

For the subgroup of infants included in placebo-controlled studies only, at low risk of all forms of bias, the need for top-up transfusions in the first week of life and thereafter was also not altered in infants

treated with IVIg (first week: 172 participants, typical RR 1.18, 95% CI 0.70 to 2.00 (Analysis 1.3.2); after first week: typical RR 1.01, 95% CI 0.80 to 1.27 (Analysis 1.5.2)) (Smits-Wintjens 2011; Santos 2013).

Smits-Wintjens 2011 and Santos 2013 were the only studies included in the analysis of the number of top-up transfusions per infant. In the first week of life and thereafter, the number of top-up transfusions was not altered in IVIg treated infants (first week: MD 0.05, 95% CI -0.07 to 0.17 (Analysis 1.4); after first week: MD -0.00, 95% CI -0.12 to 0.12 (Analysis 1.6)).

When all studies reporting these outcomes were considered, there was low to very low quality evidence (downgraded for risk of serious to very serious bias, and serious imprecision) that IVIg did not alter the risk of early or late top-up transfusion. These results were consistent with the findings of the placebo-controlled trials.

Maximum total serum bilirubin

Six studies reported results for maximum serum bilirubin (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). The meta-analysis of all six studies showed that the mean maximum serum bilirubin decreased by 25.39 µmol/L in infants receiving IVIg (MD -25.39 µmol/L, 95% CI -34.07 to -16.70) (Analysis 1.7). Furthermore, subgroup analyses showed that IVIg decreased maximum bilirubin levels in infants with Rh incompatibility, infants of more than 37 weeks of gestation, infants treated early or late, and infants treated with a single dose of IVIg. However, subgroup analyses of the only two placebo-controlled studies (Smits-Wintjens 2011; Santos 2013) and of infants born at less than 37 weeks of gestation (Smits-Wintjens 2011; Santos 2013) showed that IVIg did not reduce maximum serum bilirubin (placebo-controlled trials: MD 0.93 µmol/L, 95% CI -23.94 to 25.79 (Analysis 1.7.2); infants born at less than 37 weeks of gestation: MD -18.91 µmol/L, 95% CI -54.49 to 16.68 (data not shown)). The quality of evidence regarding maximum serum bilirubin was very low, with evidence from six randomized controlled trials downgraded for risk of bias and serious inconsistency; (heterogeneity: Chi^2 = 14.82, df = 5 (P = 0.01); I^2 = 66%). Of note, the peak serum bilirubin in the control groups varied nearly two-fold between studies, indicating that there were likely to be very different thresholds for ET between the studies.

Duration of phototherapy

Results of seven studies could be included in the meta-analysis of the duration of phototherapy (Alpay 1999; Tanyer 2001; Miqdad 2004; Nasseri 2006; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). Although all studies gave criteria for commencing phototherapy, only five studies described or provided predefined criteria for ceasing phototherapy (Alpay 1999; Tanyer 2001; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). Analysis of all seven studies showed that duration of phototherapy decreased by 0.98 days with IVIg treatment (MD -0.98 days, 95% CI -1.31 to -0.66) (Analysis 1.8). All subgroup analyses showed a decrease in duration of phototherapy in IVIg-treated infants varying from a mean decrease of 1.12 days in infants treated with a single dose of IVIg (MD -1.12 days, 95% CI -1.30 to -0.94) (Analysis 4.8) to 1.24 days in infants treated with IVIg 12 hours or less after birth (MD -1.24 days, 95% CI -1.44 to -1.03 (Analysis 3.8)). However, as for maximum bilirubin levels, analyses of the two placebo-controlled studies and of infants born less than 37 weeks of gestation showed no reduction in duration of phototherapy (placebo-controlled trials: MD -0.50 days, 95% CI -1.24 to 0.24 (Analysis 1.8.2); infants born less than 37 weeks of gestation: MD -0.91 days, 95% CI -1.96 to 0.14) (data not shown)).

Duration of hospitalization

Results of six studies could be entered in the meta-analysis (Alpay 1999; Miqdad 2004; Nasseri 2006; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). None of these studies described predefined criteria for hospital discharge and only two studies provided them through correspondence (Miqdad 2004; Santos 2013). The analysis showed that IVIg treatment shortened duration of hospitalization by 1.34 days (MD -1.34 days, 95% CI -1.60 to -1.09) (data not shown). All subgroup analyses showed a shorter duration of hospitalization with IVIg treatment (data not shown).

Incidence of adverse reactions

All studies reported or subsequently provided data on adverse reactions, although for most of the trials, we did not know any details of what protocols were used to identify adverse events or how they were defined. Nine studies reported that there were no adverse reactions of IVIg treatment (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Tanyer 2001; Miqdad 2004; Nasseri 2006; Elalfy 2011; Smits-Wintjens 2011; Santos 2013). None of the adverse reactions were necrotizing enterocolitis. In the study by Alpay 1999, two control infants receiving ET developed hypoglycemia and hypocalcemia after ET. In the study by Rübo 1992, one control infant who required ET developed sepsis and one control infant who required ET developed inspissated bile syndrome. However, the authors stated that a causal relationship with ET could not be established in either infant. In the study by Dağ oğ lu 1995, one control infant developed inspissated bile syndrome. Miqdad 2004 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." In the study by Smits-Wintjens 2011 one infant from the IVIg group developed a *Bacillus cereus* sepsis with brain abscesses a few days after ET. Sterility tests on the used IVIg batches and cultures of all donor blood products used for intrauterine transfer (IUT) and ET were sterile. The sepsis

may have been related to the umbilical venous catheterization and ET. A case report provided information on this exceptional case (Smits-Wintjens 2010).

Long-term outcomes

Only two studies had a relatively long follow-up period of one year (Santos 2013) and two years (Miqdad 2004). In both studies, there were no cases of kernicterus, deafness or cerebral palsy. All participants of the Smits-Wintjens 2011 study were included in a subsequent long-term follow-up study and neurodevelopmental outcome in children of at least two years of age was equal in children treated with IVIg and children treated with placebo (van Klink 2016). The authors stated that their findings may have been limited by a small sample size.

Neonatal mortality

None of the studies reported neonatal mortality data.

Incidence of adverse reactions possibly related to the use of intravenous immunoglobulin or exchange transfusion

None of the studies reported Incidence of adverse reactions possibly related to the use of IVIg or ET.

DISCUSSION

Summary of main results

Data from nine studies with 658 participants provided limited evidence that IVIg treatment in neonates with alloimmune HDN reduced the need for ET. Although this review update showed a significant reduction in the need for ET, most of the included studies were at high risk of bias. IVIg treatment was also associated with a significant reduction in maximum bilirubin level and duration of phototherapy when all included studies were analyzed and for most of the subgroup analyses based on type of alloimmunization, gestational age at birth, and timing and number of doses of IVIg. Duration of hospitalization was significantly reduced when analyzing all studies that reported this outcome and for almost all subgroup analyses, including the analysis of studies at low risk of bias only. Although there was some evidence that IVIg reduced hemolysis and shortened hospital stay, these results should be interpreted with considerable caution because the studies reporting these benefits were not blinded, only two studies used predefined criteria for hospital discharge, and criteria for stopping phototherapy were not reported in most studies. In addition, since the late 1980s, guidelines for phototherapy have recommended using it more promptly for infants at risk of hemolysis (Gartner 1987). 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. Seven of nine studies were included in the analysis of the incidence of top-up transfusion after the first week of life (Rübo 1992; Dağ oğ lu 1995; Alpay 1999; Miqdad 2004; Nasseri 2006; Smits-Wintjens 2011; Santos 2013). However, only five of the seven studies used predefined criteria for top-up transfusions (Alpay 1999; Miqdad 2004; Nasseri 2006; Smits-Wintjens 2011; Santos 2013). In addition, the predefined criteria varied between studies, thus conclusions were limited. Data on adverse events of IVIg seemed to indicate that it can be used safely. Although we found reports of a higher incidence of NEC in infants with HDN treated with IVIg in the literature (Corvaglia 2012; Figueras-Aloy 2010; Yang 2016), there were no cases of NEC in the current meta-analysis.

Importantly however, subgroup analysis of the only two studies that were placebo-controlled, blinded, at low risk of all forms of bias, including 172 participants, were very consistent with each other and showed that IVIg treatment had no effect on the need for ET or the number of ETs per infant (Smits-Wintjens 2011; Santos 2013). As for ET, analysis of these two studies at low risk of bias demonstrated no difference in maximum bilirubin level and duration of phototherapy.

Overall completeness and applicability of evidence

This review included all (quasi-) randomized controlled trials on the use of IVIg in alloimmune HDN. We identified 27 trials, of which nine trials, comprising 658 infants, fulfilled inclusion criteria for the review. The only two included studies that were placebo-controlled comprising a total of 172 infants, enrolled only infants with Rh HDN and the intervention consisted of a single dose of 0.5 g/kg to 0.75 g/kg IVIg administered within four to six hours after birth (Smits-Wintjens 2011; Santos 2013). Santos 2013 included infants of 32 gestational weeks or greater and Smits-Wintjens 2011 included infants of 35 gestational weeks or greater. Criteria for phototherapy and ET were similar in both studies. Evidence from subgroup analysis of these two studies with 172 participants showed that early administration of IVIg in a single dose of 0.5 g/kg to 0.75 g/kg did not reduce ETs or had other benefits in the treatment of Rh HDN. There was no clear evidence from this review that a higher dose improved 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 (Girish 2008). However, this study was not powered to detect a difference in the need for ET. Only two studies examined long-term neurodevelopmental outcome, which found no cases of kernicterus, deafness or cerebral palsy in a follow-up period of one year (Santos 2013) and two years (Miqdad 2004). All participants of the Smits-Wintjens 2011 study were included in a subsequent long-term follow-up study and neurodevelopmental outcome in children of at least two years of age was equal in children treated with IVIg and children treated with placebo (van Klink 2016).

American Academy of Pediatrics guidelines of 2004 recommend the administration of 0.5 g/kg to 1 g/kg IVIg in alloimmune HDN if TSB is rising despite intensive phototherapy or if TSB level is within 34 µmol/L to 51 µmol/L (2 to 3 mg/dL) of exchange level (AAP 2004). Based on the results of this review and because IVIg administration is not completely without risks (Copelan 1986; Magny 1991; Figueras-Aloy 2010), 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, where the risk of ET is considered to be much higher than usual, such as in very or extremely low birth weight infants, or in the context of a future research study.

Quality of the evidence

The quality of included studies ranged from fulfilling none of the 'risk of bias' criteria to fulfilling all criteria (see 'Risk of bias' section of Characteristics of included studies table, and Summary of findings for the main comparison). Only two of nine trials fulfilled all criteria to be rated as high-quality studies. We made the decision to evaluate the quality of evidence using GRADE criteria separately for the seven studies at high risk of bias and the two studies at low risk of bias, because evaluation of the seven studies at high risk of bias as a group also demonstrated other concerns including inconsistency and indirectness. For the outcomes of use and number of ETs in the first week, the quality of evidence from the seven studies at high risk of bias was very low, whereas the evidence from the two studies at low risk of bias was moderate (downgraded only for small number of participants). For the outcome of top-up transfusions after the first week, we evaluated the level of evidence only for Rh HDN and only for the two studies at low risk of bias, because we deemed this outcome to usually be irrelevant for infants with ABO incompatibility (who are at much lower risk of late anemia) and because of incomplete reporting of data in other studies. The evidence was of very low quality. Analysis of the effect of IVIg on the need for ET in infants with ABO incompatibility included only three studies at high risk of bias (Alpay 1999; Miqdad 2004; Nasseri 2006), because other studies only enrolled infants with Rh HDN, did not use predefined criteria for top-up transfusion or did not provide sufficient detail to separate Rh- and ABO-affected infants. The quality of evidence for IVIg for ABO incompatibility was very low (GRADE analysis not shown). For several of the secondary outcomes of the review, the RR (or other relevant statistic) was not estimable for included studies (no events in either intervention or control groups), highlighting the extent to which these studies were seriously underpowered. In summary, we considered that the evidence from the two trials at low risk of bias provided a sufficient quality of evidence to guide practice.

It was unclear why placebo-controlled, high-quality trials yielded such different results. Possibilities included that when administration of IVIg was not compared with use of a placebo administered in similar dose and over similar duration, there were differences in timing of the next bilirubin measurement, meaning that in IVIg-treated infants, there was longer exposure to phototherapy before the decision about ET was made. Another possibility was that there was bias in the decision to perform an ET, influenced by knowledge of group allocation. A third possibility was that rather than a specific immunomodulatory effect, IVIg (and where used, the placebo solution) has a sufficient non-specific dilutional effect to change the rate of rise of bilirubin, altering duration of exposure to phototherapy and decision making about ET.

Potential biases in the review process

We tried to minimize bias by working with two review authors 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 judgment because reviewing research is influenced by prior beliefs. In addition, one included trial was performed by two of the five 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 were consistent with previous systematic reviews. Louis 2014 included 12 studies (813 participants) and concurred with our finding that high-quality studies found no effect of IVIg, whereas low-quality studies found IVIg effective in HDN. Gottstein 2003 included three studies that were also included in our review (Rübo 1992; Dağ oğ lu 1995; Alpay 1999), and one study that was excluded from our review (Voto 1995). They concluded that with IVIg treatment significantly fewer infants required ET. Duration of hospitalization and pho-

totherapy were also significantly reduced in their review. However, based on our judgment, none of their included studies was of high quality. Two Chinese systematic reviews (Li 2010a; Li 2010b) 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. Until the date we conducted our search, our review was 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

Based on the overall outcomes of the review, there is insufficient evidence to conclude that intravenous immunoglobulin (IVIg) is beneficial in neonates with hemolytic disease of the newborn (HDN). We gave particular weight to the results of the only two studies that provide evidence at sufficient low risk of bias to guide routine clinical practice, and that show no reduction in the use of exchange transfusion (ET), or improvement in any other important outcomes of the review. In addition, IVIg has risks that have been identified in other contexts of treatment. Therefore, we believe routine use of IVIg for HDN should not be recommended.

The effect of IVIg plus phototherapy compared to phototherapy alone on eventual neurodevelopmental outcomes remains unknown, although there was no difference in neurodevelopmental outcome between these groups in a (small) long-term follow-up study (van Klink 2016). However, since there is some indirect evidence that IVIg reduces hemolysis and because it appears safe in neonates with alloimmune HDN (acknowledging that the combined sample size of all studies is insufficient to assess uncommon, put potentially serious adverse effects), 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 earliest possible use of intensive phototherapy, and 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, especially for infants for whom ET carries particularly high risks. 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 (Rath 2010). 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 placebo-controlled trials at low risk of all forms of bias, the conclusion of the review authors is that IVIg is of very limited usefulness in Rh HDN. However, neither of these placebo-controlled 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 (Murray 2007). 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 different effect in anti-A or anti-B-mediated jaundice. Due to the relative rarity of severe jaundice caused by ABO incompatibility in many countries and the fact that this condition almost always resolves with phototherapy alone (Bhat 2012), exploring the use of IVIg to treat established jaundice would require a multicenter randomized controlled trial. Based on the discordance of results in this review between trials that were conducted with and without careful blinding of the intervention using a placebo, we recommend that any future trials should either use a placebo or a robust alternative method for blinding of treatment and outcome assessment. Future trials should be well designed 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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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alpay 1999

Methods	RCT.
Participants	116 newborn term infants. ABO or Rh (or both) incompatibility. TSB > 204 µmol/L (12 mg/dL), positive direct Coombs test and reticulocyte count ≥ 10%
Interventions	Treatment group: single dose IVIg 1 g/kg (ISIVEN) plus phototherapy, started at 51.53 ± 3.5 hours (mean ± SD) after birth (n = 58). Control group: phototherapy alone, started 54.33 ± 4.0 hours (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 (Maisels 1994). Details of phototherapy: 5 blue lights (Philips F20 T12/BB) placed 30 cm above participant; body position changed periodically; no phototherapy blanket Criteria for top-up transfusions: after 15-21 days, red blood cell transfusions given because hemoglobin levels were ≤ 87 g/L * = (part of the) outcome available through correspondence.
Notes	Unpublished data and information supplied.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not stated. Method of randomization unclear despite correspondence with author. Only stated, "The attending neonatologists who made the decision regarding the choice of treatment were different from those conducting the study."
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) All outcomes	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo or other method of blinding described.

Alpay 1999 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data for all predefined 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 participants had hypoglycemia and hypocalcemia after ET
Other bias	Unclear risk	Mean bilirubin levels at study entry were already above bilirubin thresholds to invoke outcome event ET Possible sources of bias include: dilution effect of IVIg could have affected bilirubin after infusion, rate of rise of bilirubin might have been measured over different intervals, decision to prepare for ET might easily have been influenced by treatment group allocation, because of the urgency

Dağ oğ lu 1995

Methods	RCT.
Participants	45 term and preterm infants with Rh incompatibility randomized. 4 infants withdrawn postrandomization because parental consent not provided. Rh-positive infant, Rh-negative mother and positive direct Coombs test
Interventions	Treatment group: single dose IVIg 0.5 g/kg (Sandoglobulin) as soon as possible after birth (usually within 2 hours) plus phototherapy (n = 22). Control group: phototherapy alone (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 > 2000 g Criteria for phototherapy: started when bilirubin levels exceeded the relevant curves of Oski and Naiman (Oski 1982). 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. Postrandomization consent used. All infants received at least 1 IUT

Risk of bias

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."

Dağ oğ lu 1995 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Stated, "not blinded because an appropriate placebo for IVIg could not be found."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated. Contact with authors unsuccessful. Assumed blinding not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data for all predefined 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 postrandomization because consent not provided. Reasons for parental refusal not stated Some differences in IVIg and control groups despite randomization: higher boy:girl ratio in IVIg group (72% boys) than control group (47% boys) although most other characteristics did not differ. High rate of ET in control group (79%) for participants who all had IUT. ET criteria inconsistently described in Methods and Discussion of paper

Elalfy 2011

Methods	RCT.
Participants	90 term neonates (> 38 weeks of gestation) born to D-negative mothers who had not received anti-D after previous deliveries with: isoimmune HDN "proven by:" D-incompatibility between blood group of the mother and baby, a positive direct antiglobulin test and a high reticulocyte count; and significant hyperbilirubinemia requiring phototherapy in the first 12 hours of life or rising by 8.6 µmol/L/hour (0.5 mg/dL/hour) (or both) while TSB still below ET criteria on admission according to the AAP management guidelines for hyperbilirubinemia (AAP 2004).
Interventions	Treatment group 1: single dose IVIg 0.5 g/kg administered at 12 hours after birth plus phototherapy (n = 25) (number randomized 23; however, 3 moved to control group and 5 gained from high IVIg group) Treatment group 2: single dose IVIg 1 g/kg administered at 12 hours after birth plus phototherapy (n = 15) (number randomized 22; however, 2 moved to control group and 5 to low IVIg group) Control group: phototherapy alone (n = 50) (number randomized 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" (AAP 2004).

	Criteria for phototherapy: "Initiation and discontinuation of phototherapy was according to the serum bilirubin levels as provided by the AAP guidelines" (AAP 2004). Phototherapy details: 5 blue lights, of which 1 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 1 week after discharge

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	From correspondence: randomization using sealed envelopes kept in a box and shuffled. A neonatologist picked 1 envelop from box to randomize a participant
Allocation concealment (selection bias)	Low risk	See above.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No placebo or other method of blinding described. An e-mail reply to correspondence stated that study was blinded and there was no detection bias, but did 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 person who conducted the study and the person who analyzed the data
Incomplete outcome data (attrition bias) All outcomes	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 not reported in paper, but data on number of top-up transfusions in first week and thereafter were provided through correspondence. However, duration of follow-up was only until 1 week after discharge from the hospital, therefore top-up transfusions after the first week were still missing
Other bias	High risk	Significant non-random cross-over 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

Elalfy 2011 (*Continued*)

		that all parents who changed the treatment were initially randomized to the low -dose arm

Miqdad 2004

Methods	RCT.
Participants	112 neonates with "significant hyperbilirubinemia due to ABO HDN confirmed by a positive Coombs' test."
Interventions	Treatment group: single dose IVIg 0.5 g/kg plus phototherapy (9 participants received IVIg < 12 hours and 47 participants > 12 hours after birth) (n = 56) Control group: phototherapy alone (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 discontinued when TSB < 205 μmol/L (12 mg/dL). Details of phototherapy: blue fluorescent lights used (Ameda, Switzerland and Airshields, USA). Each unit had 4 lights at wavelength 460 nm. During study, they used 1 unit to denote single phototherapy, 2 units to denote double phototherapy and 3 units for triple phototherapy placed 35-40 cm above infant. They did not use phototherapy blankets Criteria for ET: if at any time TSB $\geq$ 340 μmol/L (20 mg/dL), in group, or if it was rising by $\geq$ 8.5 μmol/L/hour (0.5 mg/dL/hour) in neonates in control group Criteria for top-up transfusions: stated that no transfusions 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 approved by their hospital research committee. However, unclear from correspondence whether parental consent was given. Additional correspondence: at time they conducted the trial in Saudi Arabia there was resistance of parents and participants to consent to research in general because of misconception that participants 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."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	From correspondence: randomization by simple sampling randomization. First group of 10 participants who were numbered 1, 4, 7 and 10 were assigned to IVIg group and those numbered 2, 3, 5, 6, 8 and 9 were assigned to control group. Second group

Miqdad 2004 (*Continued*)

		of 10 participants who were numbered 1, 4, 7 and 10 were assigned to control group and those numbered 2, 3, 5, 6, 8 and 9 to 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 participants
Allocation concealment (selection bias)	Low risk	From correspondence: random number table kept by head nurse and none of treating physicians were involved in randomization process
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All data kept and entered to their database by personnel who were not involved in management of cases and that data were given to outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data for all predefined outcomes.
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported.
Other bias	High risk	Control group had additional criterion to perform ET that could have resulted in more ETs in control group. Very high rate of ET for ABO HDN in both groups, especially control group. Very high rate of clinical or culture-positive sepsis in neonates who had ET. Unclear whether neonates in each group were enrolled at similar postnatal age. Unsubstantiated claim in conclusions that IVIg worked even when given up to 72 hours of age. No data presented to support whether late vs early administration influenced efficacy

Nasseri 2006

Methods	RCT (although in Methods stated that it was a prospective case control study)
Participants	34 neonates with: gestational age of ≥ 37 weeks; positive direct Coombs test due to D or ABO incompatibility; significant hyperbilirubinemia as defined by bilirubin rising by ≥ 0.5 mg/dL/hour (8.5 μmol/L/hour); bilirubin below ET criterion on admission; and "no other risk factors such as sepsis, G6PD [glucose-6-phosphate dehydrogenase] deficiency."
Interventions	Treatment group: 3 doses IVIg 0.5 g/kg 12 hours apart within 2-4 hours of admission (mean age at admission about 20 hours) plus phototherapy (n = 17) Control group: phototherapy alone (n = 17).

Nasseri 2006 (*Continued*)

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 [neonatal intensive care unit]." 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.
Notes	

Risk of bias

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) All outcomes	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data for all predefined 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

Rübo 1992

Methods	RCT.
Participants	34 newborn infants. Rh (and Kell and Fy) incompatibility. Antigen-positive infant, antigen-negative mother and positive direct Coombs test

Rübo 1992 (*Continued*)

Interventions	Treatment group: single dose IVIg 0.5 g/kg (Polyglobin N) as soon as neonatal antigen status confirmed plus phototherapy (n = 17). Control group: phototherapy alone (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 (Polácek 1963; Polácek 1984). Criteria for phototherapy: TSB 68 µmol/L (4 mg/dL) < modified curve of Polácek (Polácek 1963; Polácek 1984). 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	2 infants excluded postrandomization because of unspecified "protocol violations." Authors contacted. No further information available

Risk of bias

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) All outcomes	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias) All outcomes	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	2 postrandomization withdrawals (1 from each group) because of protocol violations Insufficient data to determine that the 2 groups were similar at enrolment (e.g. with respect to postnatal age, sex, gestation, serum bilirubin) Described that 2 infants in IVIg group who needed an ET were treated suboptimally. Different treatment in this unblinded study?

Santos 2013

Methods	Double-blind, placebo-controlled RCT.
Participants	92 neonates: born to D-negative woman with anti-D antibodies; gestational age ≥ 32 weeks; with D-positive blood type; and with positive direct Coombs test
Interventions	Treatment group: single dose IVIg 0.5 g/kg (Immunglobulin) in 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 first hours of life and discontinued when bilirubin level < 10 mg/dL after 2 days of life. Phototherapy details: high-intensity phototherapy (irradiance > 30 IW/cm^2/nm) with blue fluorescent light (Bili-bero, 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: hematocrit < 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
Notes	Unpublished data and information supplied.

Risk of bias

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 responsible for concealment and opaque envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medication prepared by pharmacist and applied such that parents, nurses and pediatricians were blinded to its identity (IVIg vs placebo)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Intervention blinded as described above and investigators and treating clinicians were different groups

Santos 2013 (*Continued*)

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

Smits-Wintjens 2011

Methods	Double-blind, placebo-controlled RCT.
Participants	80 neonates ≥ 35 weeks of gestation. HDN caused by anti-D or anti-c antibodies of D-negative or c-negative mother with positive direct Coombs test. Maternal antibody-dependent cellular cytotoxicity test > 50% (comparable with Indirect Antiglobulin Test titer 1:64)
Interventions	Treatment group: single dose 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 (AAP 2004) 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 (AAP 2004). Phototherapy details: intensive phototherapy using white light with intensity 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: hemoglobin 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.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated, sequence code kept by chief pharmacist.

Smits-Wintjens 2011 (*Continued*)

Allocation concealment (selection bias)	Low risk	Pharmacy-controlled block randomization.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical coded drug boxes and vials. 1 infant's treatment unblinded due to serious adverse event. Unblinding unlikely to have affected study outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Sequence code broken after 3-month follow-up period of last included participant
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data for all predefined outcomes.
Selective reporting (reporting bias)	Low risk	Some outcomes not completely reported as described in published protocol. In protocol, described that changes in bilirubin in first 24 and 48 hours (%) would be measured. Paper only described bilirubin levels at birth and maximum bilirubin during admission. In protocol, described that top-up transfusions would be measured in first week of life and after first week until 3 months of life. Paper described top-up transfusions for whole period until 3 months after birth. However, data on changes in bilirubin levels were available and data on the top-up transfusion were provided for first week and thereafter separately, therefore rated at low risk of bias
Other bias	Low risk	1 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

Methods	Quasi-randomized trial.
Participants	61 neonates with 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 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)

Tanyer 2001 (*Continued*)

	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 started once participant was admitted to clinic and stopped when bilirubin level "decreased to the safe limit." Details phototherapy: performed using white quartz halogen lamp (Air Shields Microlite Phototherapy system) with a distance between infant and light source of 41 cm Criteria for ET: performed when bilirubin levels exceeded the accepted limits (shown in Table 1 of paper with reference to Bryla 1985).
Notes	

Risk of bias

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) All outcomes	High risk	No placebo or other method of blinding described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo or other method of blinding described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data for all predefined outcomes.
Selective reporting (reporting bias)	High risk	Duration of hospitalization and top-up transfusions not reported

AAP: American Academy of Pediatrics; ET: exchange transfusion; HDN: hemolytic disease of the newborn; IUT: intrauterine transfer; IVIg: intravenous immunoglobulin; n: number of participants; RCT: randomized controlled trial; SD: standard deviation; TSB: total serum bilirubin.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Atici 1996	RCT compared single dose IVIg plus phototherapy with phototherapy alone. Even after receiving additional information from the authors, much remained unclear on study design and enrolment criteria. Top-up transfusions not reported. Furthermore, unclear whether parents of participants gave consent and no statement on ethics approval made
Garcia 2004	Randomized, double-blind, placebo-controlled pilot trial including 18 participants (11 IVIg and 7 controls). Published as meeting abstract and subsequent study was never performed to our knowledge. Available abstract did not report predefined criteria for primary outcome of ET (1 of inclusion criteria for this review). Information remained unavailable after communication with authors
Girish 2008	RCT compared 2 doses of IVIg and had no placebo or 'standard care' control group
Hematyar 2011	RCT compared maximum of 3 doses of IVIg with control (phototherapy only). Despite additional information supplied by author, important information for support of bias judgment remained unavailable. Top-up transfusions, number of ETs and adverse events not reported
Huang 2006	Study did not report predefined criteria for the primary outcome ET. Despite additional information supplied by author, important information for support of bias judgment remained unavailable
Liu 2016	No English full text available. After translating the Chinese article, many criteria for bias judgment remained unclear and our attempt to retrieve additional information from authors was unsuccessful
Pishva 2000	Paper not available in full text and previous attempt to retrieve additional information from authors was unsuccessful. Therefore, 4/7 criteria for bias judgment remained unclear. Top-up transfusions not reported. Correspondence with authors seemed unlikely to yield further information given interval since report, abstract only (no paper) and previous unsuccessful attempt
Rübo 1996	RCT compared 2 different IVIg regimens with phototherapy alone. Very high risk of bias as study groups were not equal at baseline (higher bilirubin levels in control group). Protocol violations led to 2 postrandomization withdrawals, unclear from which group. 4 control group infants were treated with IVIg and analyzed likewise, no intention to treat analysis done. Data on duration of hospitalization stay and duration of phototherapy lacking
Spinelli 2001	Abstract selectively reported outcome for enrolled infants who had moderate-severe hemolysis. Criteria for severity not stated although stratification into mild, moderate and severe was predefined. Correspondence with authors seems unlikely to yield further information given interval since report, abstract only (no full paper) and previous unsuccessful attempt
Voto 1995	RCT compared single dose of IVIg with control. However, none of the outcomes were reported in usable form for meta-analysis. Top-up transfusions and ET were not separately reported, bilirubin levels were presented as graphs rather than tables, and although the mean durations of phototherapy and hospitalization were presented in a table, the measure of variance was unclear. Correspondence with authors seems unlikely to yield further information given interval since report and previous unsuccessful attempt
Wang 2002	Study did not report predefined criteria for the primary outcome ET and our attempt to retrieve additional information from the authors was unsuccessful

ET: exchange transfusion; IVIg: intravenous immunoglobulin; RCT: randomized controlled trial.

DATA AND ANALYSES

Comparison 1. Intravenous immunoglobulin plus phototherapy versus phototherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of exchange transfusion (≥ 1)	9	658	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.25, 0.49]
1.1 Studies without a placebo group	7	486	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.18, 0.39]
1.2 Placebo-controlled studies	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.48, 1.98]
2 Exchange transfusions per infant, by study quality	9	658	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.50, -0.17]
2.1 Studies without a placebo group	7	486	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.64, -0.25]
2.2 Placebo-controlled studies	2	172	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.18, 0.10]
3 Use of top-up transfusion in 1st week by study quality	4	378	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.65, 1.69]
3.1 Studies without a placebo group	2	206	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.24, 2.12]
3.2 Placebo-controlled studies	2	172	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.70, 2.00]
4 Top-up transfusions in 1st week per infant by study quality	3	262	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
4.1 Studies without a placebo group	1	90	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
5 Use of top-up transfusion after 1st week by study quality	7	507	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.97, 1.38]
5.1 Studies without a placebo group	5	335	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.08, 1.82]
5.2 Placebo-controlled studies	2	172	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.80, 1.27]
6 Top-up transfusions after first week per infant, by study quality	4	316	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]
6.1 Studies without a placebo group	2	144	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]
7 Maximum total serum bilirubin (µmol/L) by study quality	6	451	Mean Difference (IV, Fixed, 95% CI)	-25.39 [-34.07, -16.70]
7.1 Studies without a placebo group	4	279	Mean Difference (IV, Fixed, 95% CI)	-29.05 [-38.32, -19.78]
7.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	0.93 [-23.94, 25.79]
8 Duration of phototherapy (days) by study quality	7	585	Mean Difference (IV, Random, 95% CI)	-0.98 [-1.31, -0.66]
8.1 Studies without a placebo group	5	413	Mean Difference (IV, Random, 95% CI)	-1.06 [-1.41, -0.72]
8.2 Placebo-controlled studies	2	172	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.24, 0.24]

Comparison 2. Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of exchange transfusion (≥ 1)	7	371	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.25, 0.58]
1.1 Studies without a placebo group	5	199	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.13, 0.40]
1.2 Placebo-controlled studies	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.48, 1.98]
2 Exchange transfusions per infant	7	371	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.34, -0.16]
2.1 Studies without a placebo group	5	199	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.51, -0.28]
2.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.18, 0.10]
3 Use top-up transfusion in 1st week	4	285	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.65, 1.77]
3.1 Studies without a placebo group	2	113	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.10, 2.51]
3.2 Placebo-controlled studies	2	172	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.70, 2.00]
4 Top-up transfusions in 1st week per infant	3	262	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
4.1 Studies without a placebo group	1	90	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
5 Use of top-up transfusion after 1st week	6	281	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.92, 1.28]
5.1 Studies without a placebo group	4	109	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.96, 1.53]
5.2 Placebo-controlled studies	2	172	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.80, 1.27]
6 Top-up transfusions after 1st week per infant	3	204	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]
7 Maximum total serum bilirubin (µmol/L)	6	358	Mean Difference (IV, Fixed, 95% CI)	-21.77 [-30.86, -12.67]
7.1 Studies without a placebo group	4	186	Mean Difference (IV, Fixed, 95% CI)	-25.27 [-35.04, -15.50]
7.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	0.92 [-23.94, 25.79]
8 Duration of phototherapy (days)	5	298	Mean Difference (IV, Fixed, 95% CI)	-1.23 [-1.43, -1.02]
8.1 Studies without a placebo group	3	126	Mean Difference (IV, Fixed, 95% CI)	-1.28 [-1.49, -1.07]
8.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.24, 0.24]

Comparison 3. Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of exchange transfusion (≥ 1)	5	335	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.26, 0.66]
1.1 Studies without a placebo group	3	163	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.11, 0.42]
1.2 Placebo-controlled studies	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.48, 1.98]
2 Exchange transfusions per infant	5	335	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.28, -0.10]
2.1 Studies without a placebo group	3	163	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.42, -0.18]
2.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.18, 0.10]
3 Use of top-up transfusion in 1st week	3	262	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.70, 2.00]
4 Top-up transfusions in 1st week per infant	3	262	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
5 Use of top-up transfusions after 1st week	4	245	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.89, 1.22]
6 Top-up transfusions after 1st week per infant	3	204	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]
7 Maximum total serum bilirubin (µmol/L)	5	335	Mean Difference (IV, Fixed, 95% CI)	-20.57 [-29.81, -11.33]
7.1 Studies without a placebo group	3	163	Mean Difference (IV, Fixed, 95% CI)	-24.01 [-33.96, -14.06]
7.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	0.92 [-23.94, 25.79]
8 Duration of phototherapy (days)	3	262	Mean Difference (IV, Fixed, 95% CI)	-1.24 [-1.44, -1.03]
8.1 Studies without a placebo group	1	90	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-1.51, -1.09]
8.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.24, 0.24]

Comparison 4. Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of exchange transfusion (≥ 1)	7	563	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.26, 0.53]
1.1 Studies without a placebo group	5	391	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.17, 0.42]
1.2 Placebo-controlled studies	2	172	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.48, 1.98]
2 Exchange transfusions per infant	7	563	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.28, -0.14]
2.1 Studies without a placebo group	5	391	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.36, -0.19]
2.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.18, 0.10]

3 Use of top-up transfusions in 1st week	4	378	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.65, 1.69]
4 Top-up transfusions in 1st week per infant	3	262	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.07, 0.17]
5 Use of top-up transfusion after 1st week	6	473	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.95, 1.33]
6 Top-up transfusions after 1st week per infant	4	316	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.12, 0.12]
7 Maximum total serum bilirubin (µmol/L)	6	451	Mean Difference (IV, Fixed, 95% CI)	-25.39 [-34.07, -16.70]
7.1 Studies without a placebo group	4	279	Mean Difference (IV, Fixed, 95% CI)	-29.05 [-38.32, -19.78]
7.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	0.92 [-23.94, 25.79]
8 Duration of phototherapy (days)	5	490	Mean Difference (IV, Fixed, 95% CI)	-1.12 [-1.30, -0.94]
8.1 Studies without a placebo group	3	318	Mean Difference (IV, Fixed, 95% CI)	-1.16 [-1.34, -0.97]
8.2 Placebo-controlled studies	2	172	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.24, 0.24]

Comparison 5. Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Multiple doses of IVIg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of exchange transfusion (≥ 1)	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.09, 0.81]
2 Exchange transfusions per infant	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.94 [-1.45, -0.43]
3 Use of top-up transfusions after 1st week	1	34	Odds Ratio (M-H, Fixed, 95% CI)	5.65 [0.25, 126.87]
4 Duration of phototherapy (days)	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.47 [-2.52, -0.42]

Comparison 6. Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of exchange transfusion (≥ 1)	6	391	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.25, 0.61]
1.1 Studies without a placebo group	4	301	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.18, 0.49]
1.2 Placebo-controlled studies	2	90	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.49, 6.42]
2 Exchange transfusions per infant	6	391	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.26, -0.08]
2.1 Studies without a placebo group	4	301	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.36, -0.15]
2.2 Placebo-controlled studies	2	90	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.12, 0.22]

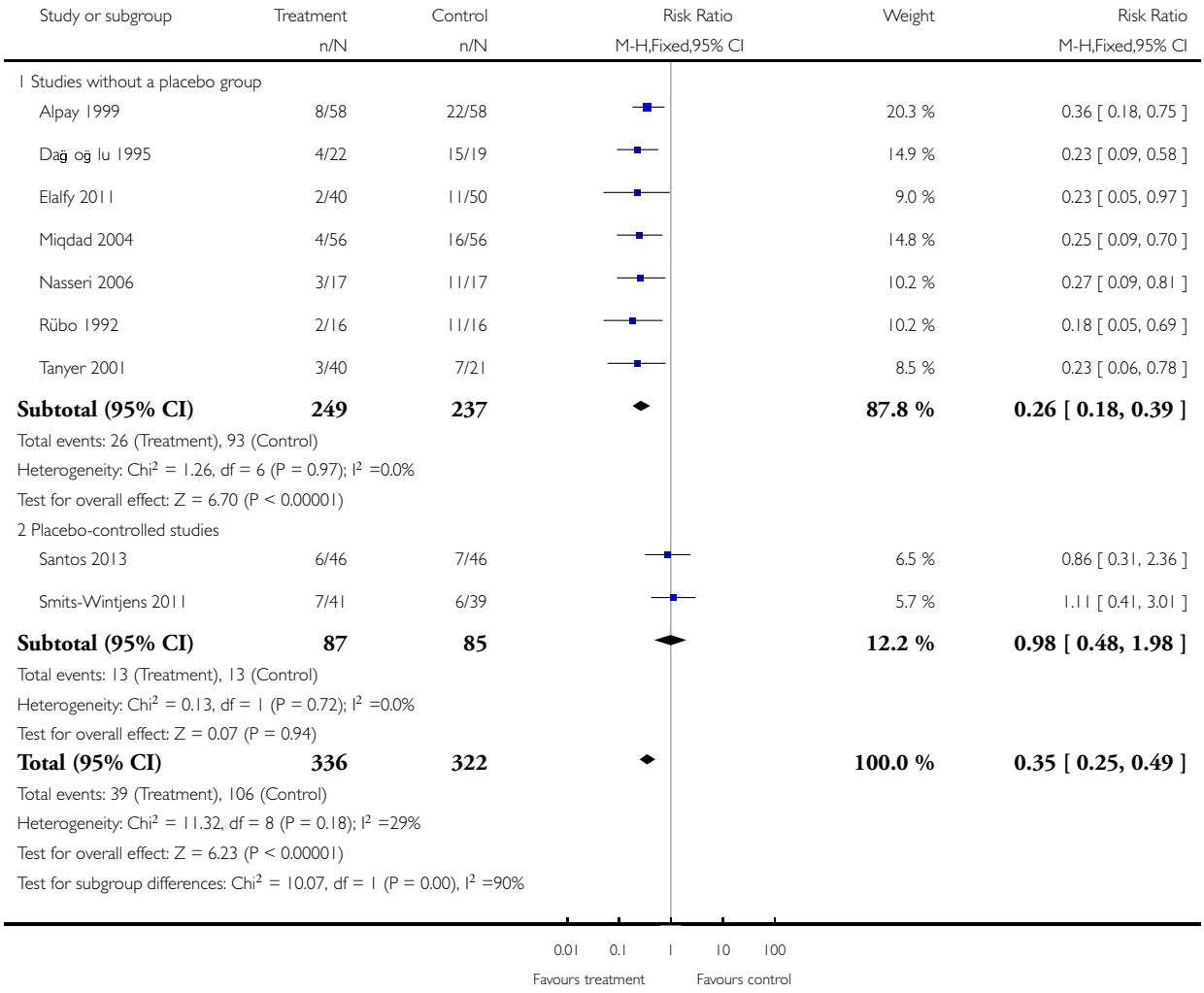
3 Use of top-up transfusion in 1st week	4	296	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.48, 1.74]
4 Top-up transfusions in 1st week per infant	3	180	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.35, 0.33]
5 Use of top-up transfusion after 1st week	4	240	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.81, 1.71]
6 Top-up transfusions after 1st week per infant	2	90	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.20, 0.13]
7 Maximum total serum bilirubin (µmol/L)	4	296	Mean Difference (IV, Fixed, 95% CI)	-26.81 [-35.97, -17.65]
7.1 Studies without a placebo group	2	206	Mean Difference (IV, Fixed, 95% CI)	-30.33 [-39.83, -20.82]
7.2 Placebo-controlled studies	2	90	Mean Difference (IV, Fixed, 95% CI)	19.47 [-15.00, 53.94]
8 Duration of phototherapy (days)	6	391	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-1.38, -1.01]
8.1 Studies without a placebo group	4	301	Mean Difference (IV, Fixed, 95% CI)	-1.25 [-1.44, -1.06]
8.2 Placebo-controlled studies	2	90	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.75, 1.12]
9 Duration of hospitalization (days)	5	330	Mean Difference (IV, Fixed, 95% CI)	-1.33 [-1.59, -1.07]
9.1 Studies without a placebo group	3	240	Mean Difference (IV, Fixed, 95% CI)	-1.37 [-1.63, -1.10]
9.2 Placebo-controlled studies	2	90	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-1.69, 1.05]

Analysis 1.1. Comparison 1 Intravenous immunoglobulin plus phototherapy versus phototherapy, Outcome 1 Use of exchange transfusion (≥ 1).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 1 Intravenous immunoglobulin plus phototherapy versus phototherapy

Outcome: 1 Use of exchange transfusion (≥ 1)

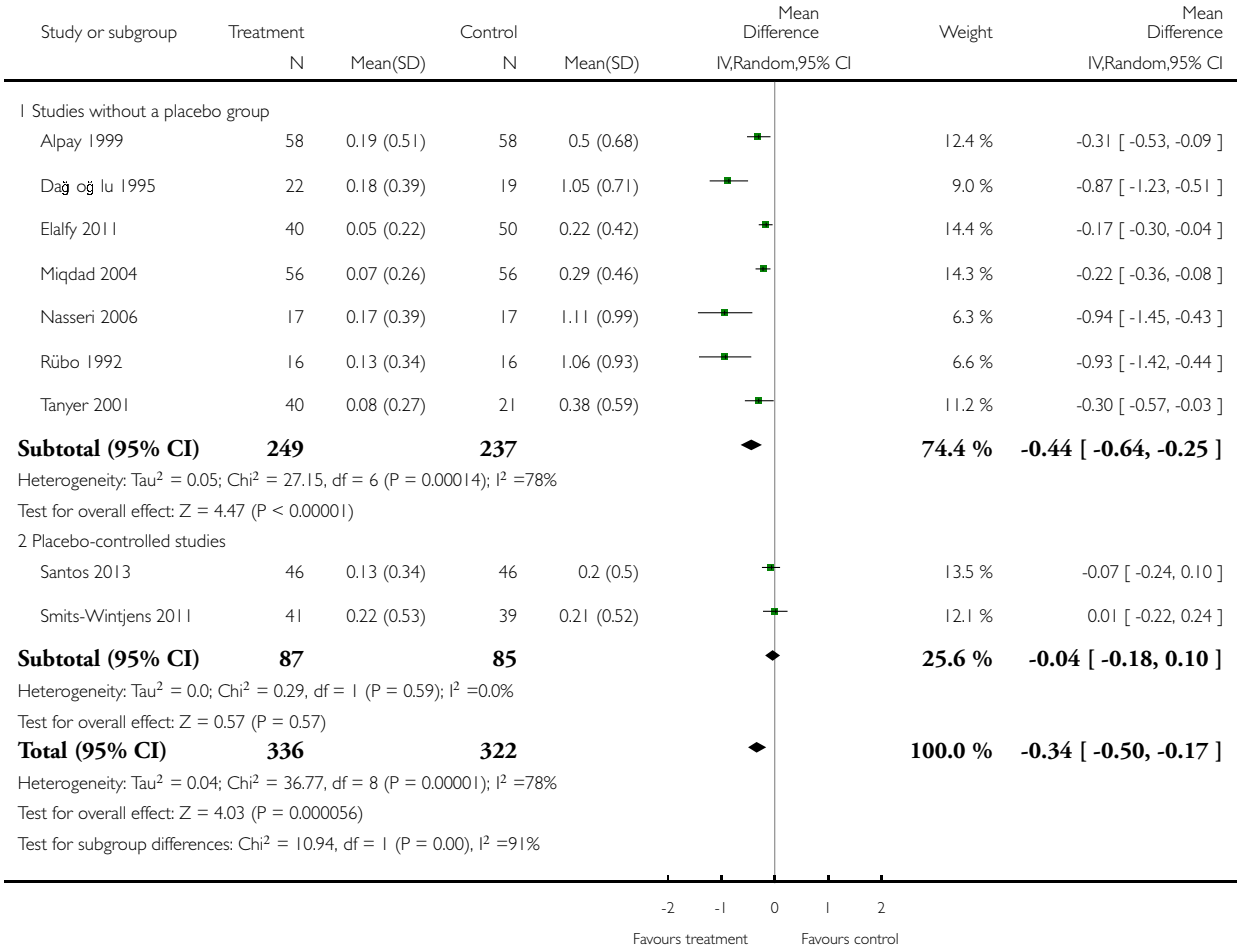


Analysis 1.2. Comparison 1 Intravenous immunoglobulin plus phototherapy versus phototherapy, Outcome 2 Exchange transfusions per infant, by study quality.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 1 Intravenous immunoglobulin plus phototherapy versus phototherapy

Outcome: 2 Exchange transfusions per infant, by study quality

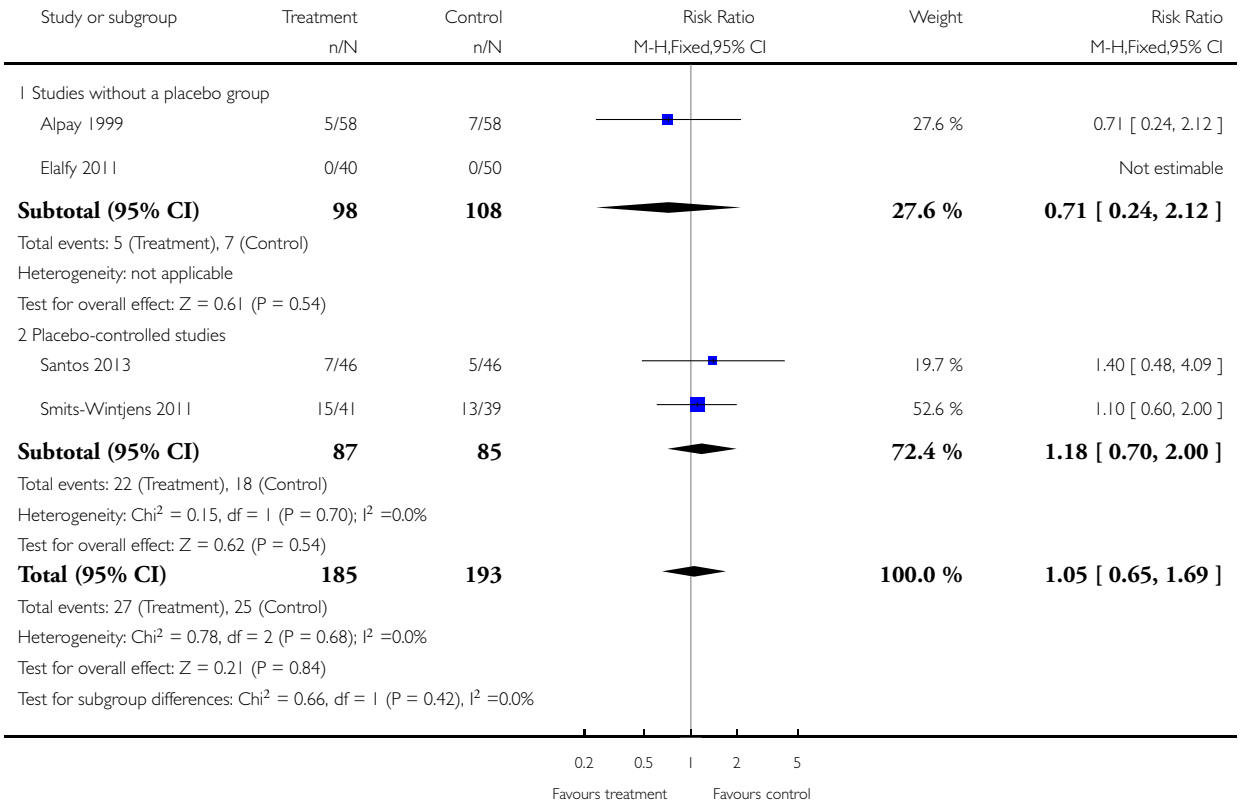


Analysis 1.3. Comparison 1 Intravenous immunoglobulin plus phototherapy versus phototherapy, Outcome 3 Use of top-up transfusion in 1st week by study quality.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 1 Intravenous immunoglobulin plus phototherapy versus phototherapy

Outcome: 3 Use of top-up transfusion in 1st week by study quality



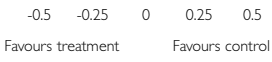
Analysis 1.4. Comparison 1 Intravenous immunoglobulin plus phototherapy versus phototherapy, Outcome 4 Top-up transfusions in 1st week per infant by study quality.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 1 Intravenous immunoglobulin plus phototherapy versus phototherapy

Outcome: 4 Top-up transfusions in 1st week per infant by study quality

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Studies without a placebo group							
Elalfy 2011	40	0 (0)	50	0 (0)			Not estimable
Subtotal (95% CI)	**40**		**50**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Placebo-controlled studies							
Santos 2013	46	0.15 (0.36)	46	0.11 (0.32)		74.1 %	0.04 [-0.10, 0.18]
Smits-Wintjens 2011	41	0.41 (0.59)	39	0.33 (0.48)		25.9 %	0.08 [-0.16, 0.32]
Subtotal (95% CI)	**87**		**85**			**100.0 %**	**0.05 [-0.07, 0.17]**
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.77); I^2 =0.0%							
Test for overall effect: Z = 0.82 (P = 0.41)							
Total (95% CI)	**127**		**135**			**100.0 %**	**0.05 [-0.07, 0.17]**
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.77); I^2 =0.0%							
Test for overall effect: Z = 0.82 (P = 0.41)							
Test for subgroup differences: Not applicable							

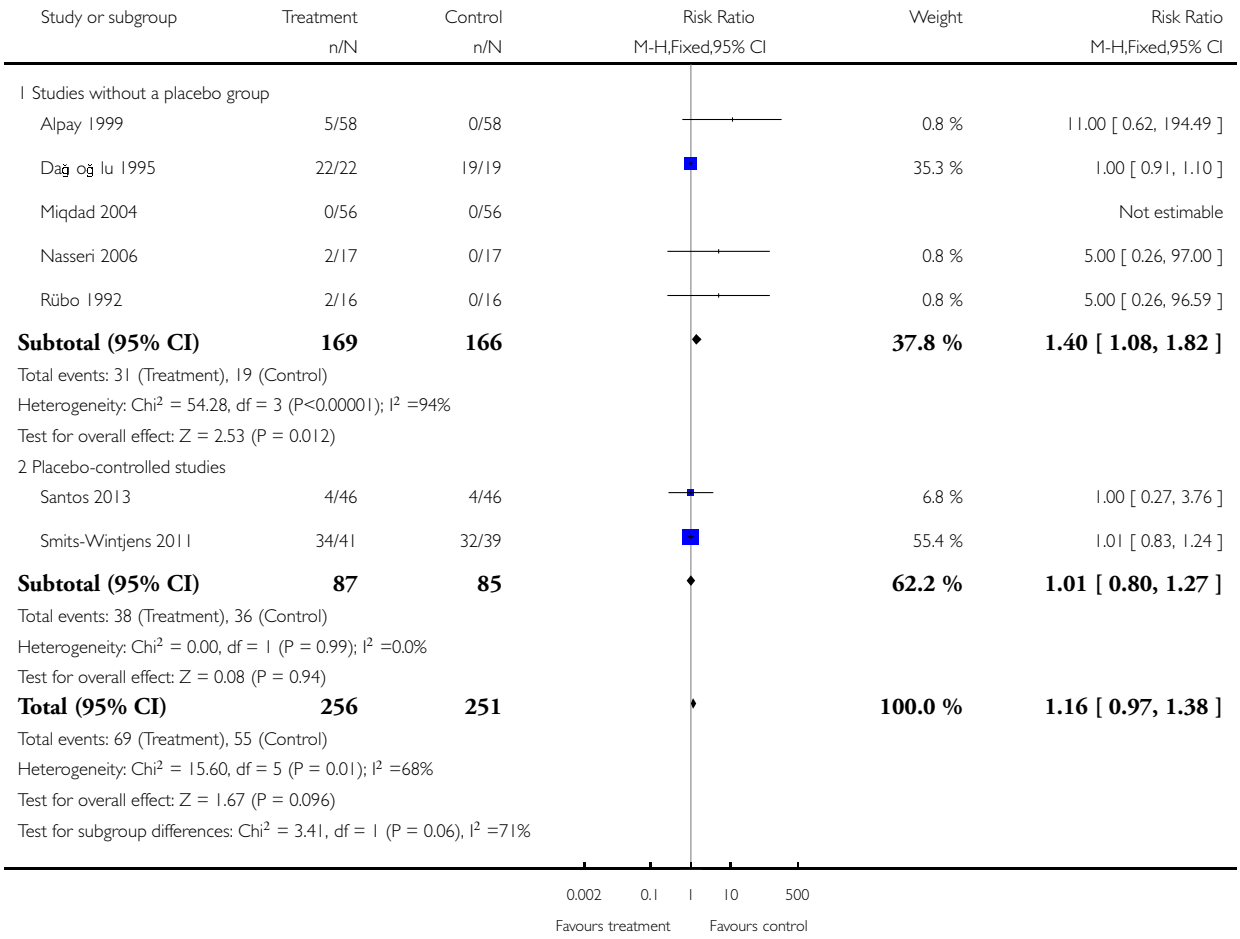


Analysis 1.5. Comparison 1 Intravenous immunoglobulin plus phototherapy versus phototherapy, Outcome 5 Use of top-up transfusion after 1st week by study quality.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 1 Intravenous immunoglobulin plus phototherapy versus phototherapy

Outcome: 5 Use of top-up transfusion after 1st week by study quality



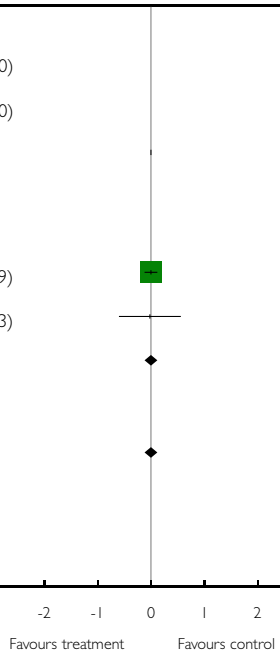
Analysis 1.6. Comparison 1 Intravenous immunoglobulin plus phototherapy versus phototherapy, Outcome 6 Top-up transfusions after first week per infant, by study quality.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 1 Intravenous immunoglobulin plus phototherapy versus phototherapy

Outcome: 6 Top-up transfusions after first week per infant, by study quality

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Studies without a placebo group							
Miqdad 2004	56	0 (0)	56	0 (0)			Not estimable
Rübo 1992	16	0.19 (0.54)	16	0 (0)			Not estimable
Subtotal (95% CI)	**72**		**72**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Placebo-controlled studies							
Santos 2013	46	0.09 (0.29)	46	0.09 (0.29)		96.0 %	0.0 [-0.12, 0.12]
Smits-Wintjens 2011	41	1.83 (1.32)	39	1.85 (1.33)		4.0 %	-0.02 [-0.60, 0.56]
Subtotal (95% CI)	**87**		**85**			**100.0 %**	**0.00 [-0.12, 0.12]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 0.01 (P = 0.99)							
Total (95% CI)	**159**		**157**			**100.0 %**	**0.00 [-0.12, 0.12]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%							
Test for overall effect: Z = 0.01 (P = 0.99)							
Test for subgroup differences: Not applicable							

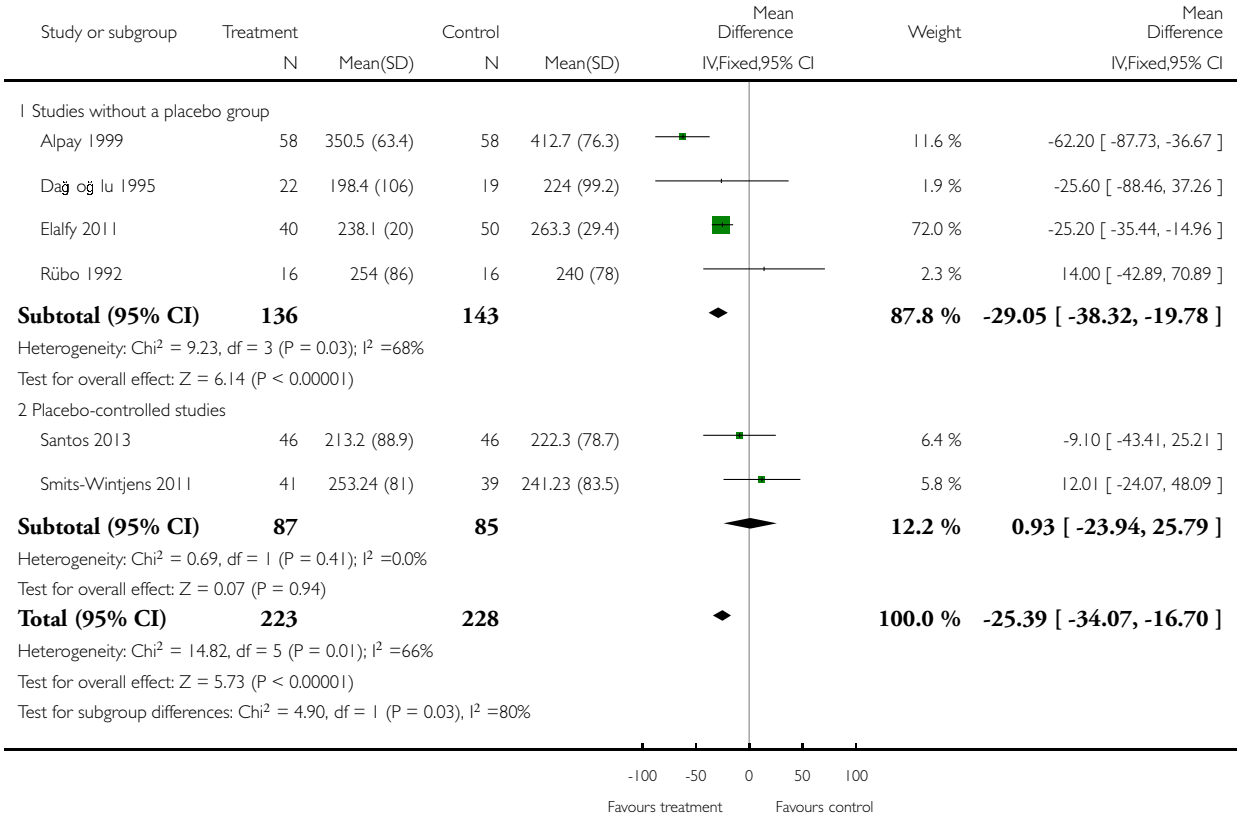


Analysis 1.7. Comparison 1 Intravenous immunoglobulin plus phototherapy versus phototherapy, Outcome 7 Maximum total serum bilirubin (µmol/L) by study quality.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 1 Intravenous immunoglobulin plus phototherapy versus phototherapy

Outcome: 7 Maximum total serum bilirubin (mol/L) by study quality

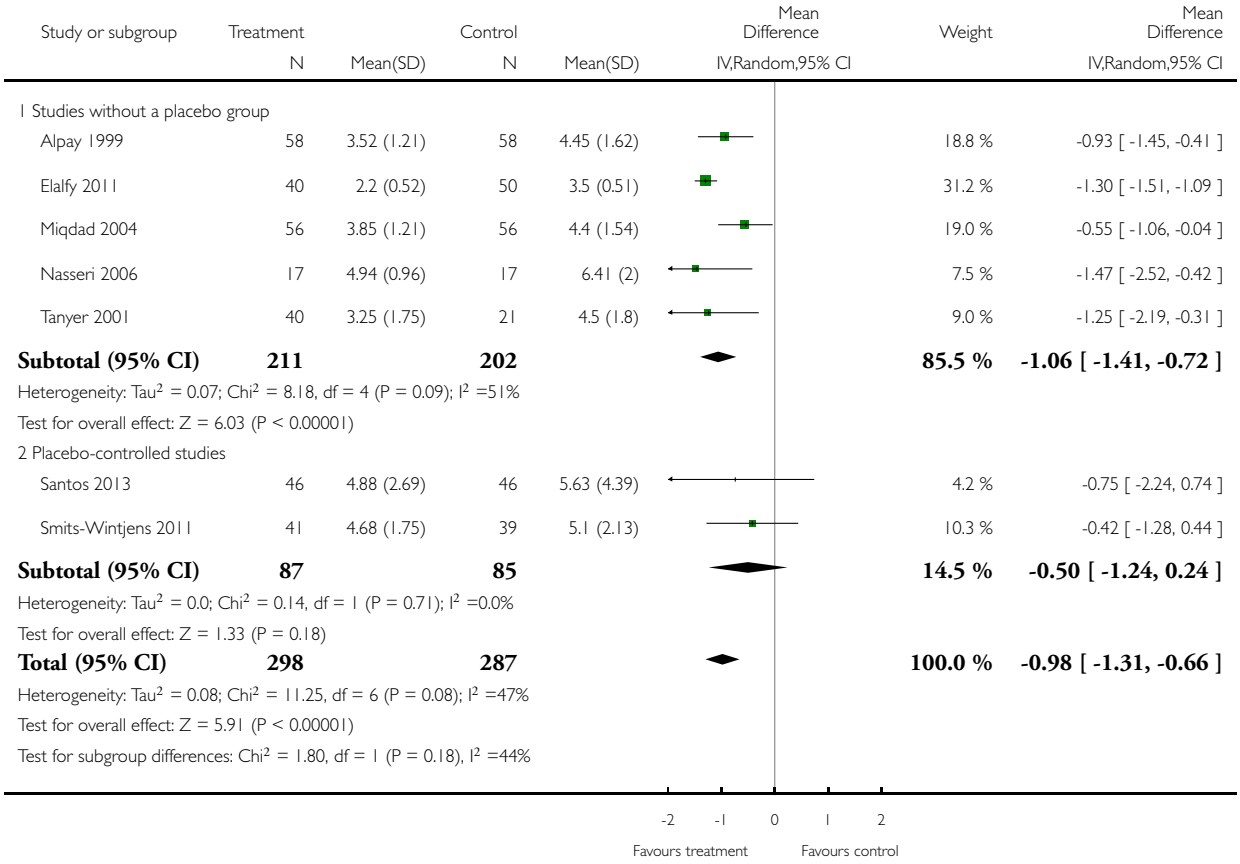


Analysis 1.8. Comparison 1 Intravenous immunoglobulin plus phototherapy versus phototherapy, Outcome 8 Duration of phototherapy (days) by study quality.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 1 Intravenous immunoglobulin plus phototherapy versus phototherapy

Outcome: 8 Duration of phototherapy (days) by study quality

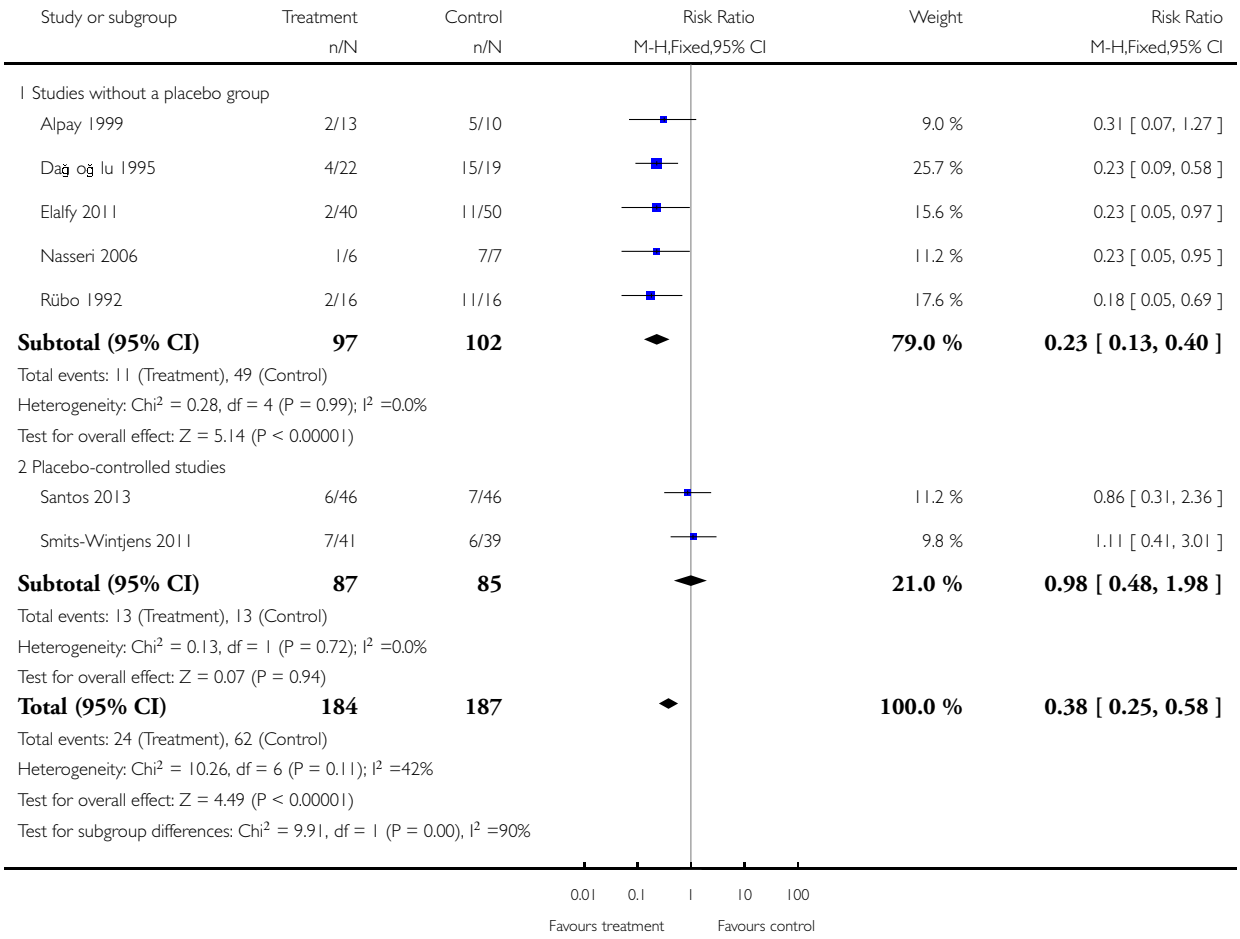


Analysis 2.1. Comparison 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only, Outcome 1 Use of exchange transfusion (≥ 1).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only

Outcome: 1 Use of exchange transfusion (≥ 1)

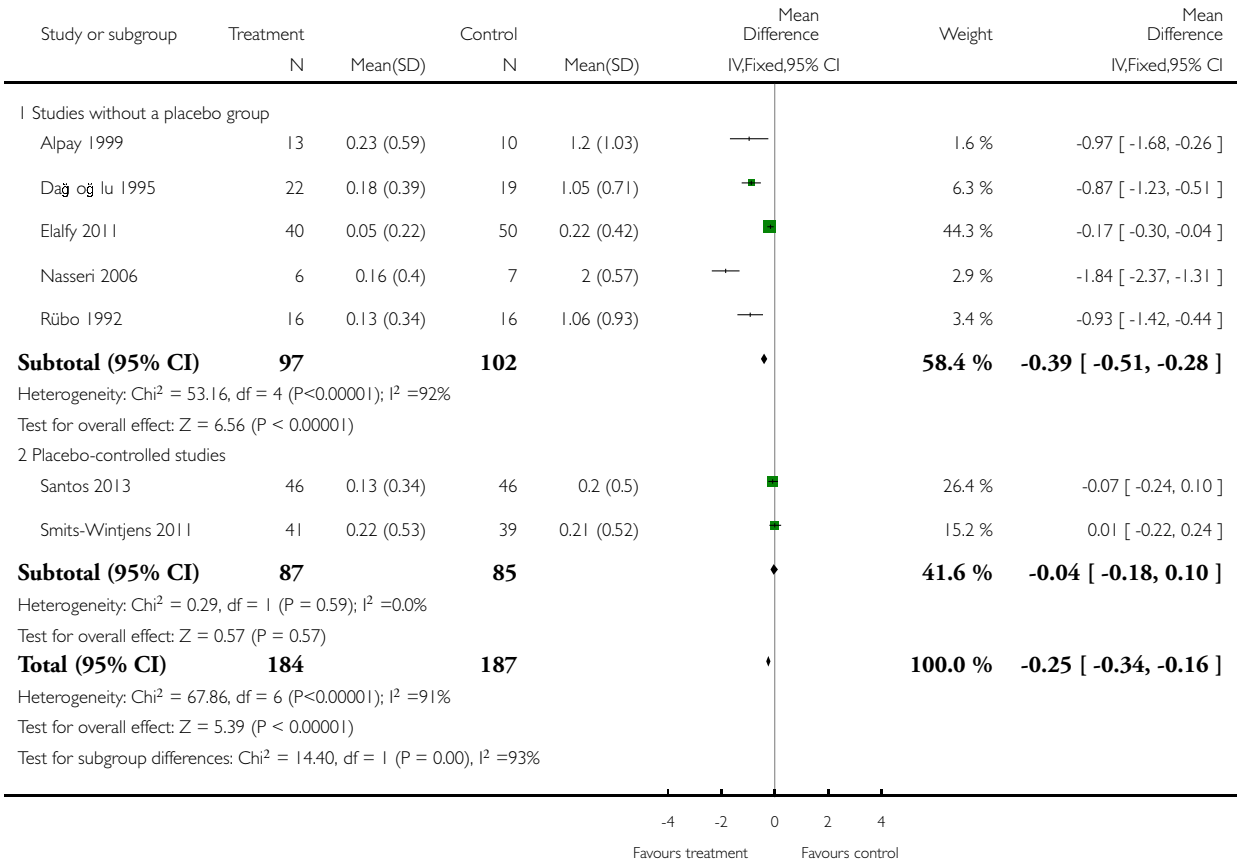


Analysis 2.2. Comparison 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only, Outcome 2 Exchange transfusions per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only

Outcome: 2 Exchange transfusions per infant

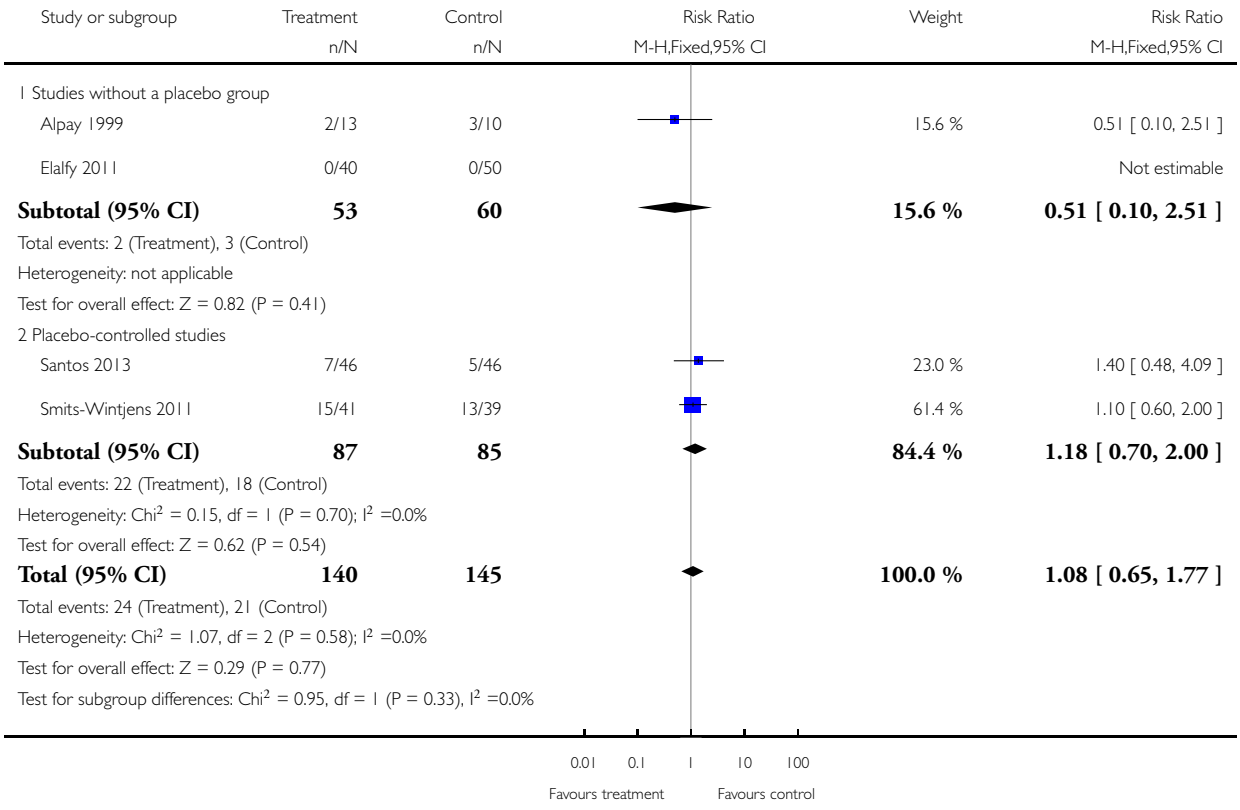


Analysis 2.3. Comparison 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only, Outcome 3 Use top-up transfusion in 1st week.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only

Outcome: 3 Use top-up transfusion in 1st week

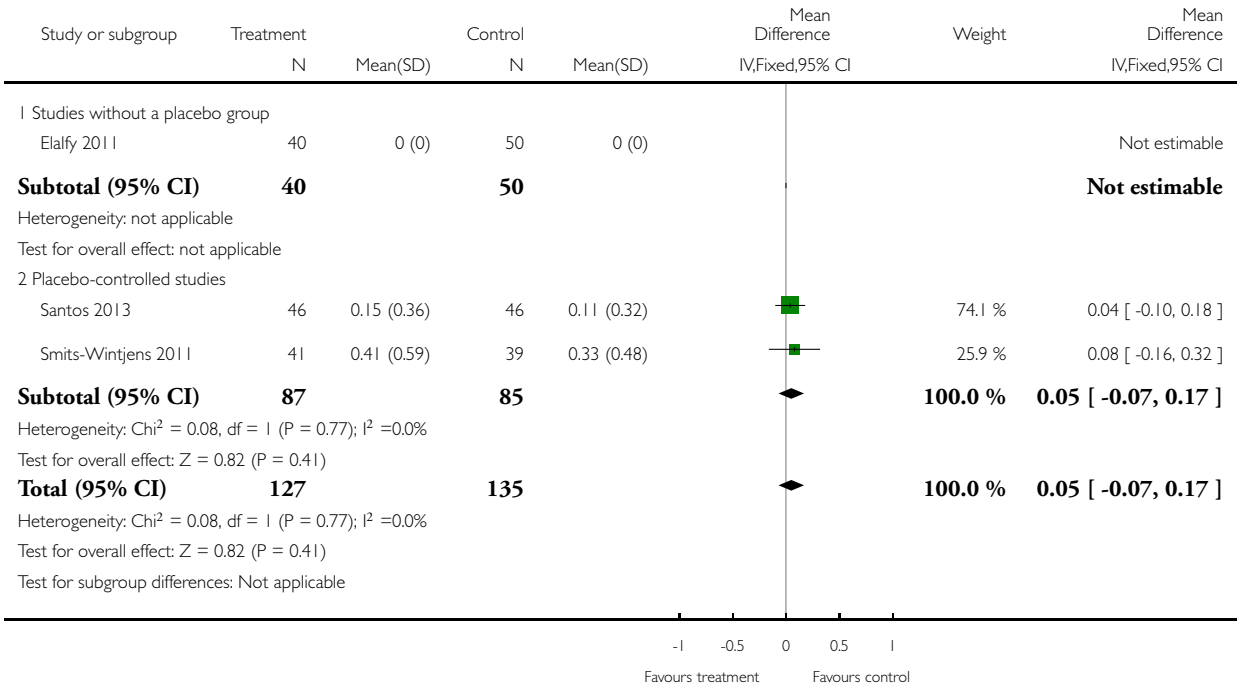


Analysis 2.4. Comparison 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only, Outcome 4 Top-up transfusions in 1st week per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only

Outcome: 4 Top-up transfusions in 1st week per infant

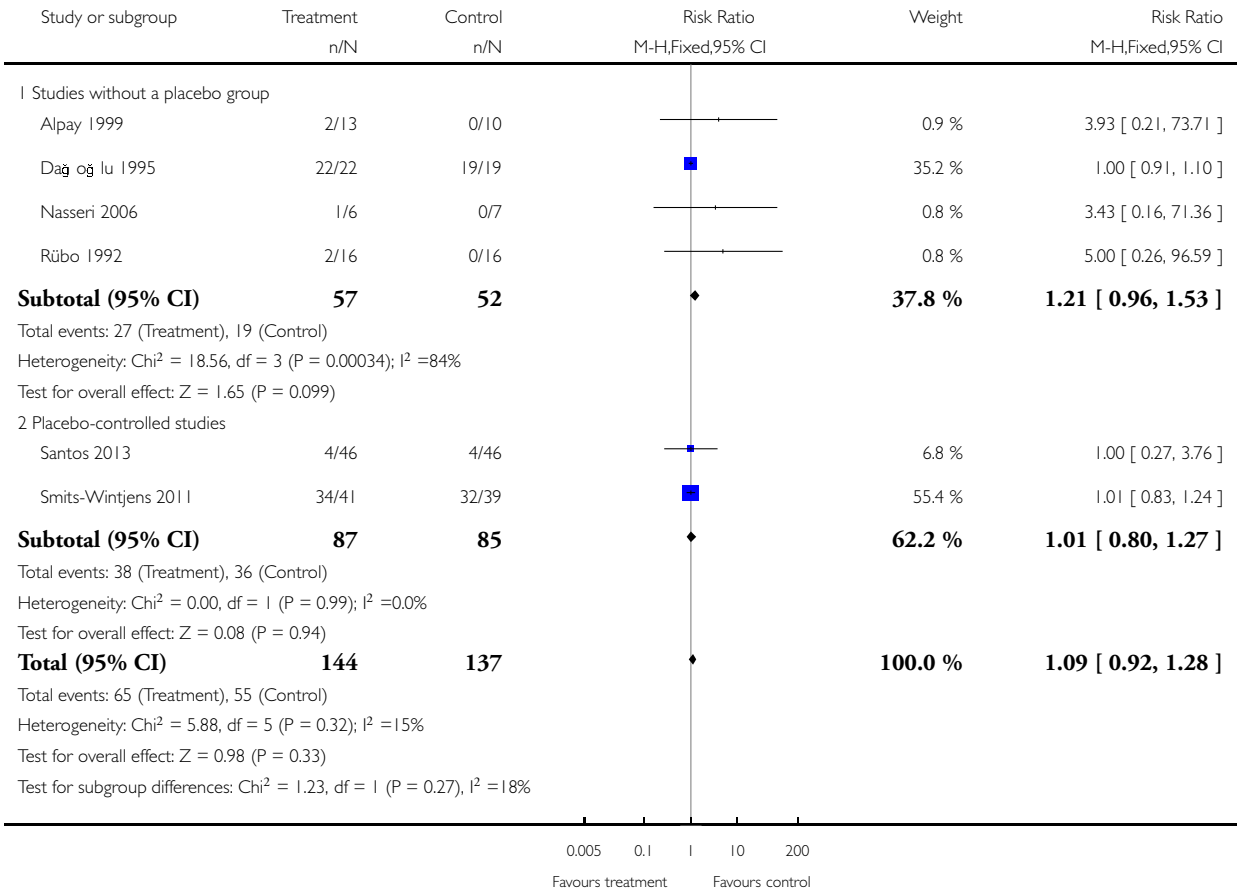


Analysis 2.5. Comparison 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only, Outcome 5 Use of top-up transfusion after 1st week.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only

Outcome: 5 Use of top-up transfusion after 1st week



Analysis 2.6. Comparison 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only, Outcome 6 Top-up transfusions after 1st week per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only

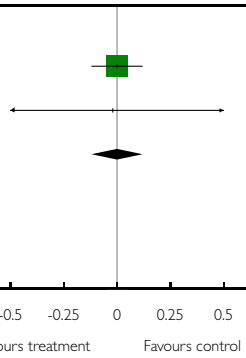
Outcome: 6 Top-up transfusions after 1st week per infant

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Rübo 1992	16	0.19 (0.54)	16	0 (0)			Not estimable
Santos 2013	46	0.09 (0.29)	46	0.09 (0.29)		96.0 %	0.0 [-0.12, 0.12]
Smits-Wintjens 2011	41	1.83 (1.32)	39	1.85 (1.33)		4.0 %	-0.02 [-0.60, 0.56]
Total (95% CI)	**103**		**101**			**100.0 %**	**0.00 [-0.12, 0.12]**

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable

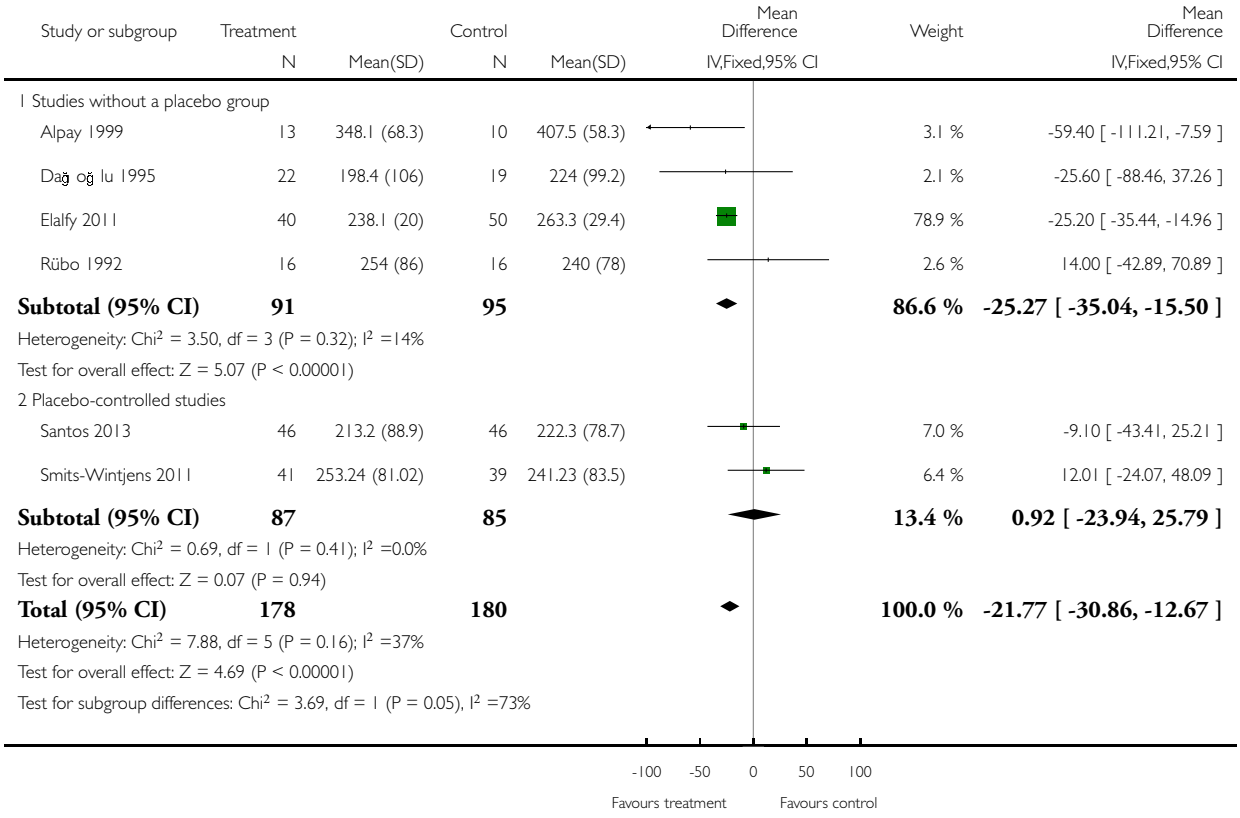


Analysis 2.7. Comparison 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only, Outcome 7 Maximum total serum bilirubin (µmol/L).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only

Outcome: 7 Maximum total serum bilirubin (mol/L)



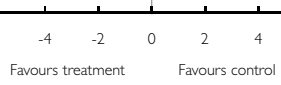
Analysis 2.8. Comparison 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only, Outcome 8 Duration of phototherapy (days).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 2 Intravenous immunoglobulin plus phototherapy versus phototherapy. Rh incompatibility only

Outcome: 8 Duration of phototherapy (days)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Studies without a placebo group							
Alpay 1999	13	3.28 (1.26)	10	3.71 (1.48)		3.1 %	-0.43 [-1.57, 0.71]
Elalfy 2011	40	2.2 (0.52)	50	3.5 (0.51)		87.6 %	-1.30 [-1.51, -1.09]
Nasseri 2006	6	5.33 (1.03)	7	7.14 (1.57)		2.0 %	-1.81 [-3.24, -0.38]
Subtotal (95% CI)	**59**		**67**			**92.7 %**	**-1.28 [-1.49, -1.07]**
Heterogeneity: Chi^2 = 2.68, df = 2 (P = 0.26); I^2 =25%							
Test for overall effect: Z = 12.06 (P < 0.00001)							
2 Placebo-controlled studies							
Santos 2013	46	4.88 (2.69)	46	5.63 (4.39)		1.8 %	-0.75 [-2.24, 0.74]
Smits-Wintjens 2011	41	4.68 (1.75)	39	5.1 (2.13)		5.5 %	-0.42 [-1.28, 0.44]
Subtotal (95% CI)	**87**		**85**			**7.3 %**	**-0.50 [-1.24, 0.24]**
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%							
Test for overall effect: Z = 1.33 (P = 0.18)							
Total (95% CI)	**146**		**152**			**100.0 %**	**-1.23 [-1.43, -1.02]**
Heterogeneity: Chi^2 = 6.75, df = 4 (P = 0.15); I^2 =41%							
Test for overall effect: Z = 11.97 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.93, df = 1 (P = 0.05), I^2 =75%							

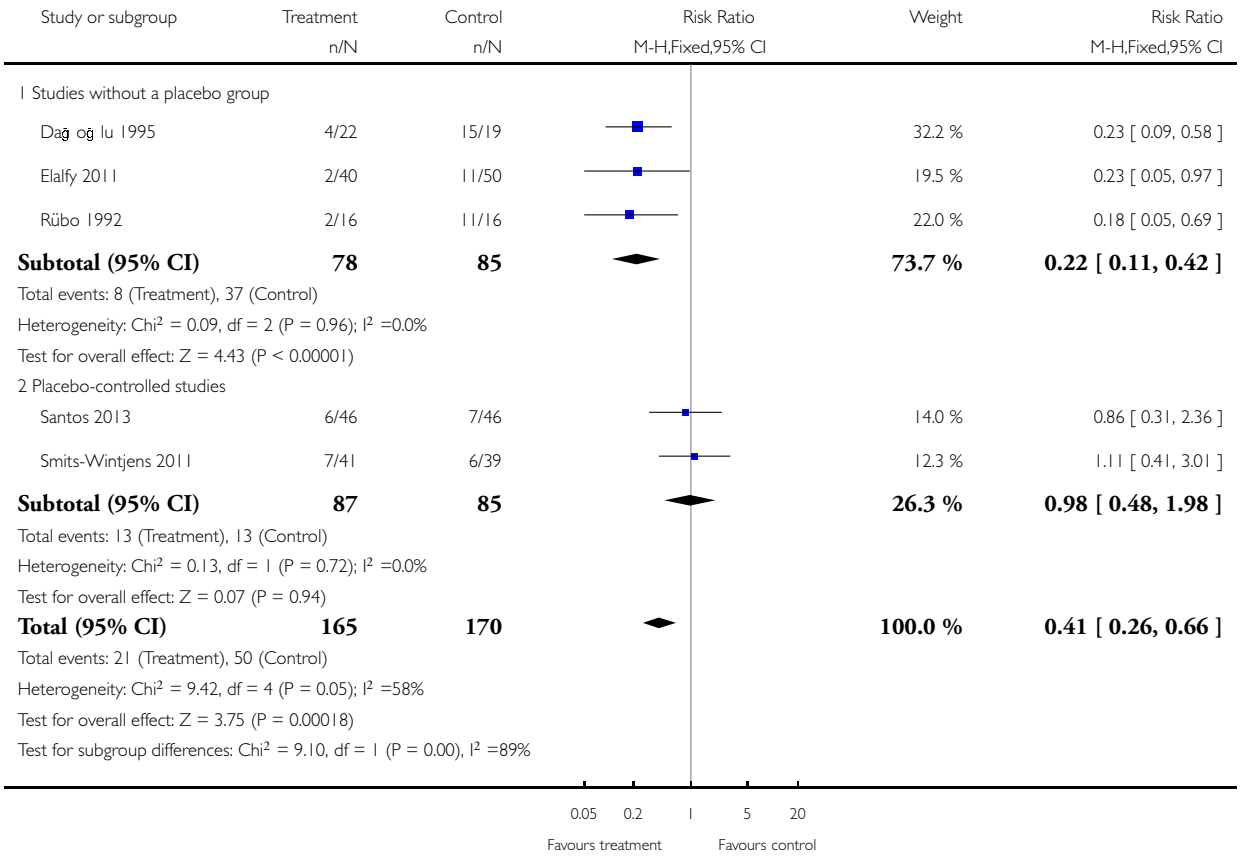


Analysis 3.1. Comparison 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth, Outcome 1 Use of exchange transfusion (≥ 1).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth

Outcome: 1 Use of exchange transfusion (≥ 1)

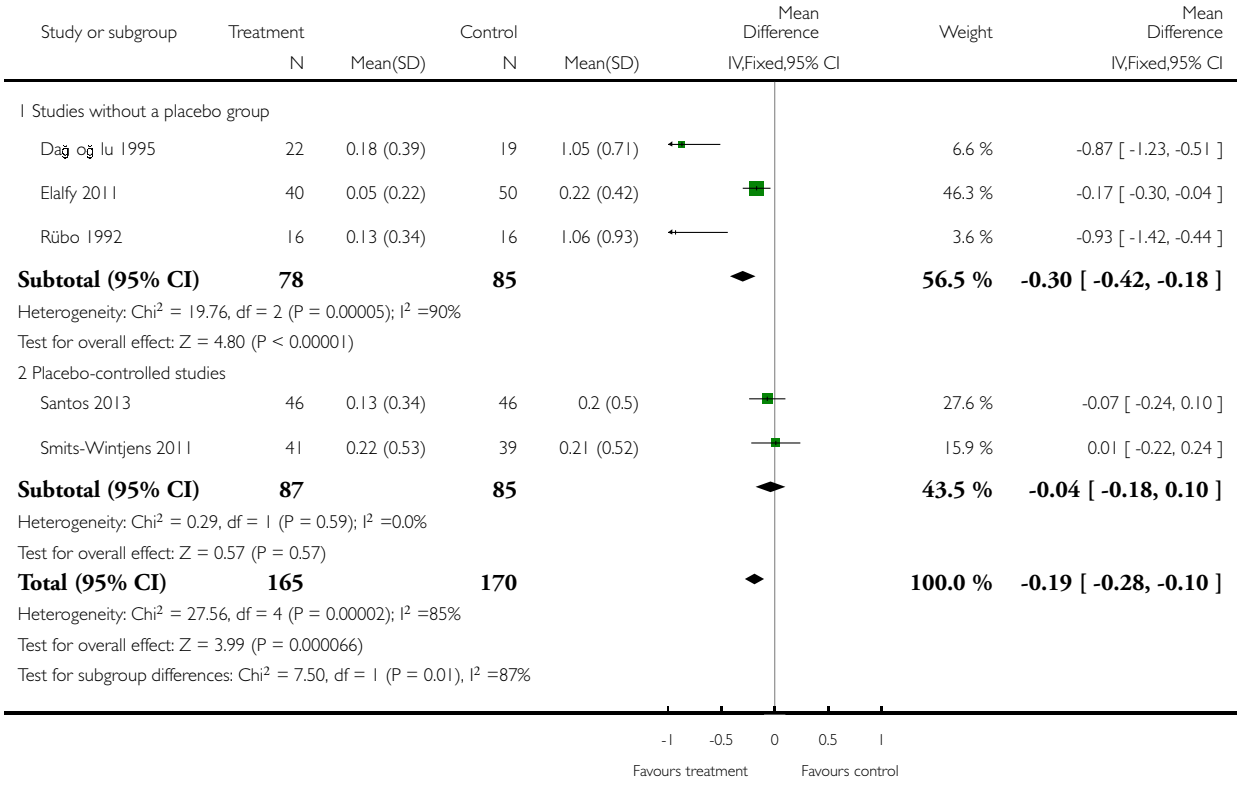


Analysis 3.2. Comparison 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth, Outcome 2 Exchange transfusions per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth

Outcome: 2 Exchange transfusions per infant



Analysis 3.3. Comparison 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth, Outcome 3 Use of top-up transfusion in 1st week.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth

Outcome: 3 Use of top-up transfusion in 1st week

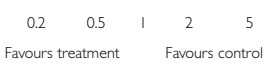
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Elalfy 2011	0/40	0/50			Not estimable
Santos 2013	7/46	5/46		27.3 %	1.40 [0.48, 4.09]
Smits-Wintjens 2011	15/41	13/39		72.7 %	1.10 [0.60, 2.00]
Total (95% CI)	**127**	**135**		**100.0 %**	**1.18 [0.70, 2.00]**

Total events: 22 (Treatment), 18 (Control)

Heterogeneity: $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.62 (P = 0.54)

Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth, Outcome 4 Top-up transfusions in 1st week per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth

Outcome: 4 Top-up transfusions in 1st week per infant

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Elalfy 2011	40	0 (0)	50	0 (0)			Not estimable
Santos 2013	46	0.15 (0.36)	46	0.11 (0.32)		74.1 %	0.04 [-0.10, 0.18]
Smits-Wintjens 2011	41	0.41 (0.59)	39	0.33 (0.48)		25.9 %	0.08 [-0.16, 0.32]
Total (95% CI)	**127**		**135**			**100.0 %**	**0.05 [-0.07, 0.17]**

Heterogeneity: $Chi^2 = 0.08$, df = 1 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable

Analysis 3.5. Comparison 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth, Outcome 5 Use of top-up transfusions after 1st week.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth

Outcome: 5 Use of top-up transfusions after 1st week

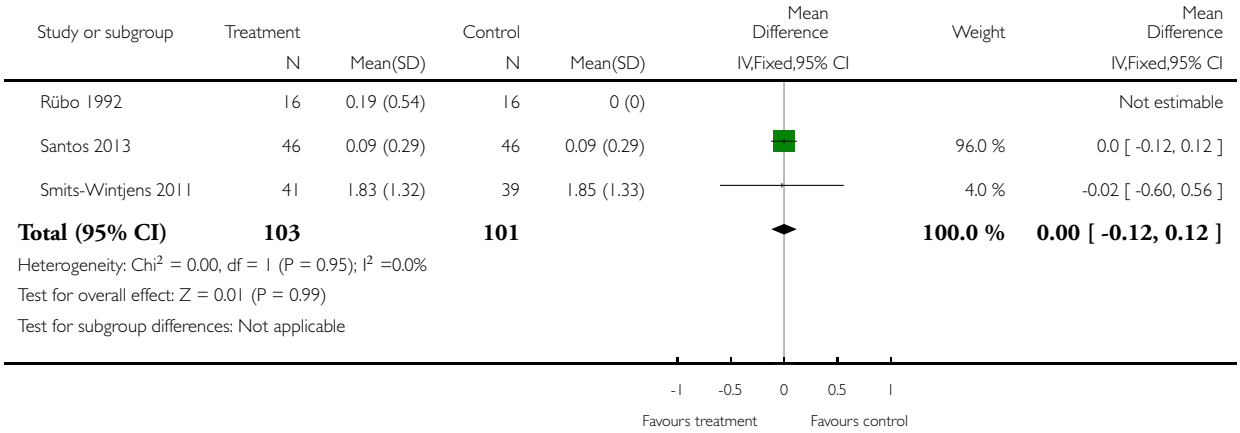
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dağ oğ lu 1995	22/22	19/19		35.9 %	1.00 [0.91, 1.10]
Rübo 1992	2/16	0/16		0.9 %	5.00 [0.26, 96.59]
Santos 2013	4/46	4/46		6.9 %	1.00 [0.27, 3.76]
Smits-Wintjens 2011	34/41	32/39		56.4 %	1.01 [0.83, 1.24]
Total (95% CI)	**125**	**120**		**100.0 %**	**1.04 [0.89, 1.22]**
Total events: 62 (Treatment), 55 (Control)					
Heterogeneity: Chi^2 = 1.86, df = 3 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.49 (P = 0.62)					
Test for subgroup differences: Not applicable					

Analysis 3.6. Comparison 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth, Outcome 6 Top-up transfusions after 1st week per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth

Outcome: 6 Top-up transfusions after 1st week per infant

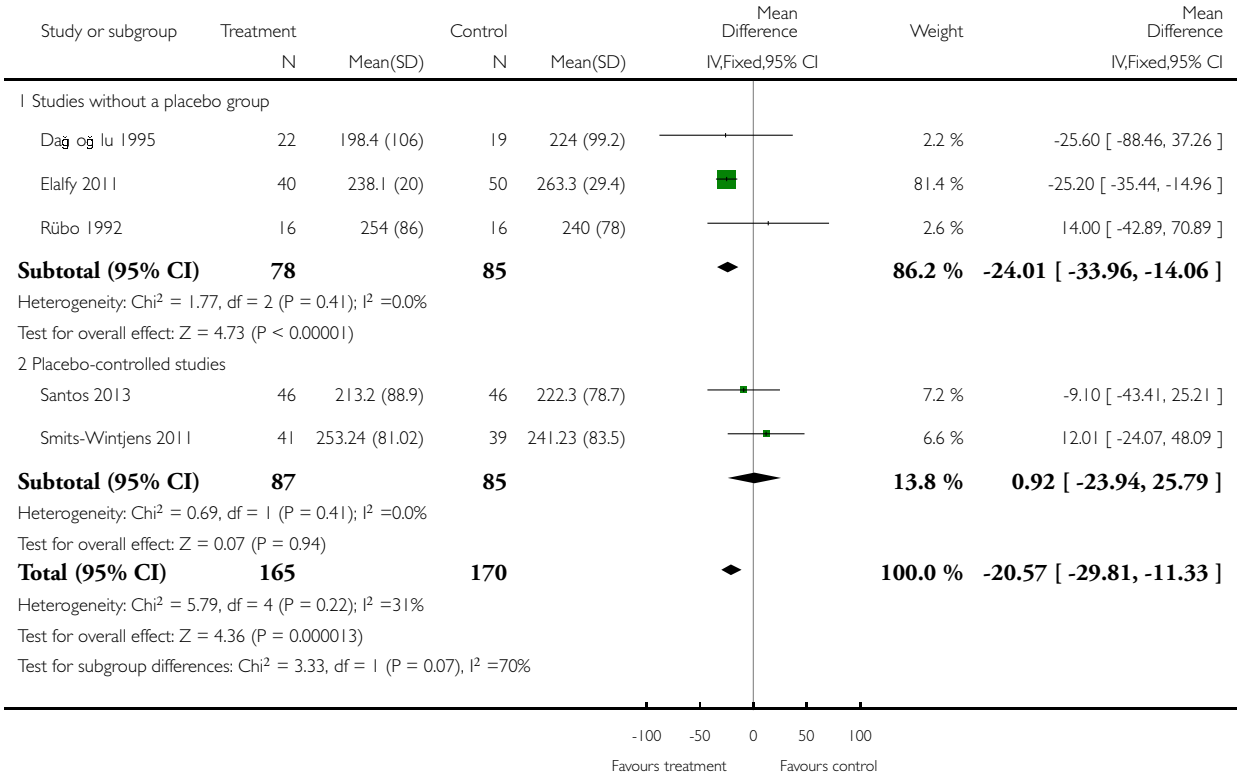


Analysis 3.7. Comparison 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth, Outcome 7 Maximum total serum bilirubin (µmol/L).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth

Outcome: 7 Maximum total serum bilirubin (mol/L)

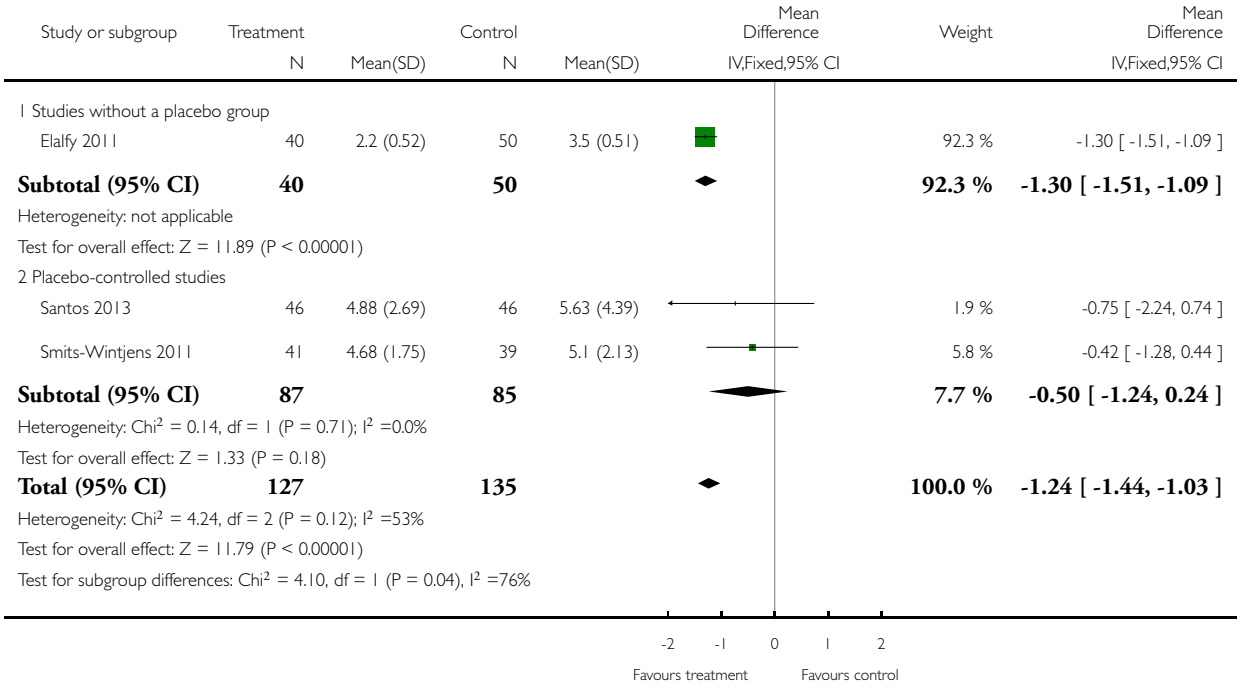


Analysis 3.8. Comparison 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth, Outcome 8 Duration of phototherapy (days).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 3 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. IVIg administration ≤ 12 hours after birth

Outcome: 8 Duration of phototherapy (days)

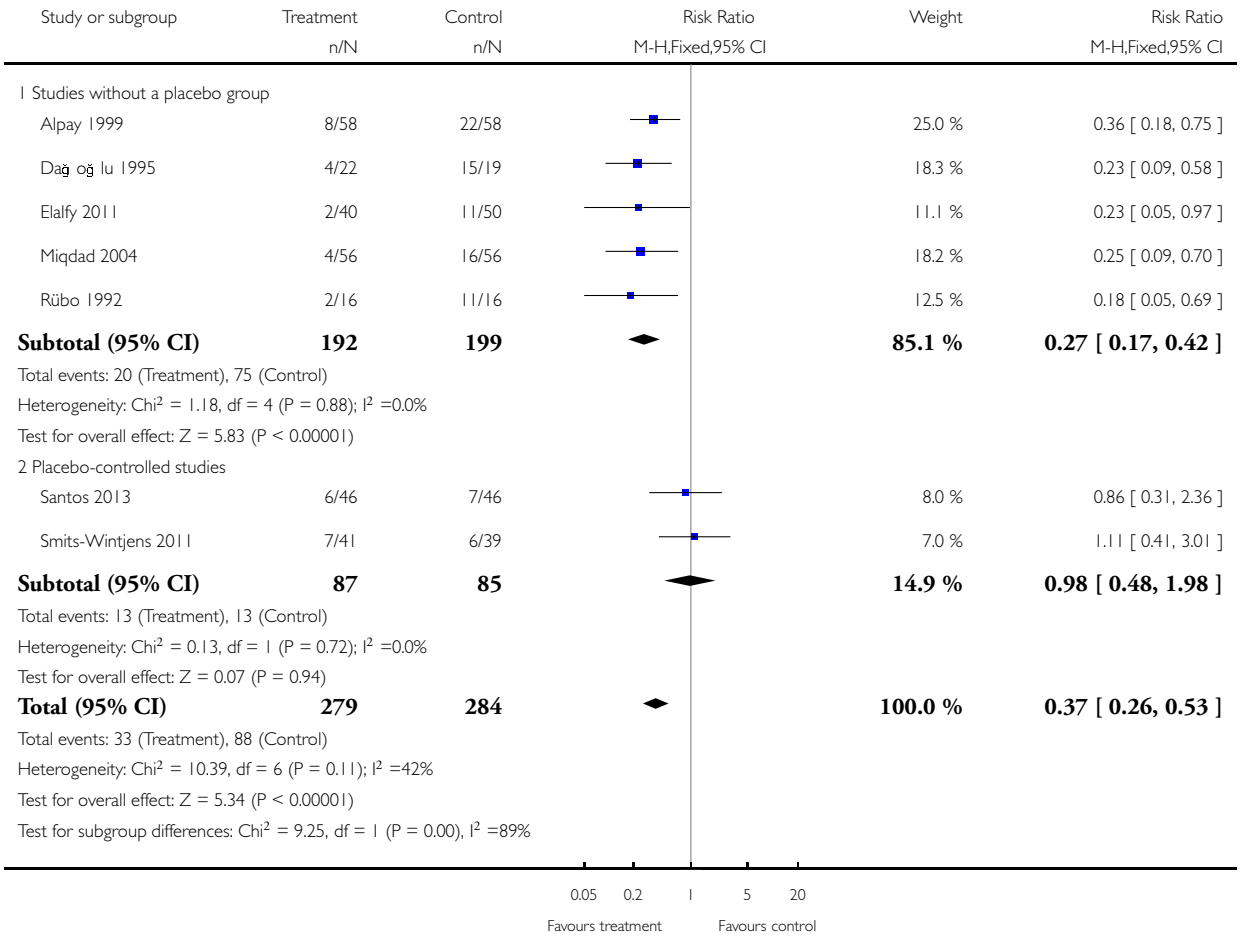


Analysis 4.1. Comparison 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg, Outcome 1 Use of exchange transfusion (≥ 1).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg

Outcome: 1 Use of exchange transfusion (≥ 1)

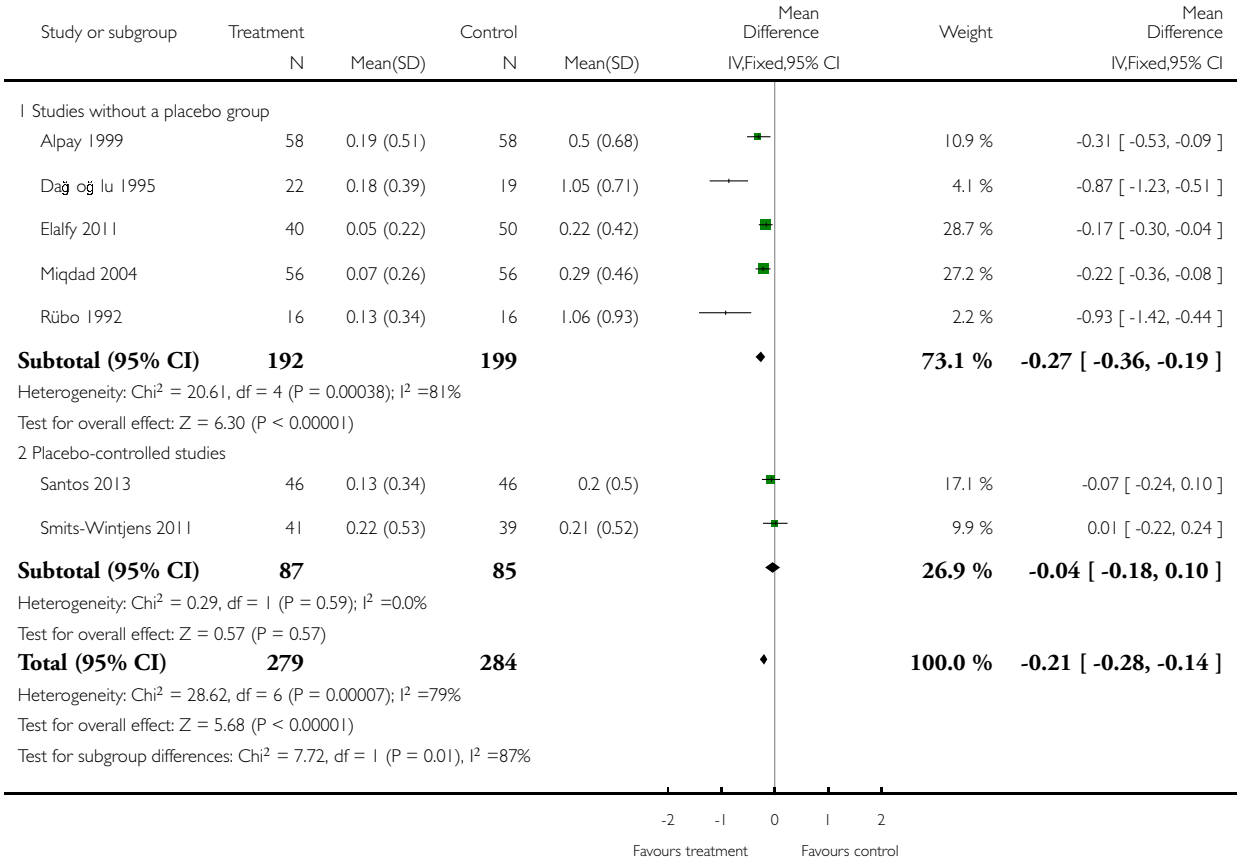


Analysis 4.2. Comparison 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg, Outcome 2 Exchange transfusions per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg

Outcome: 2 Exchange transfusions per infant

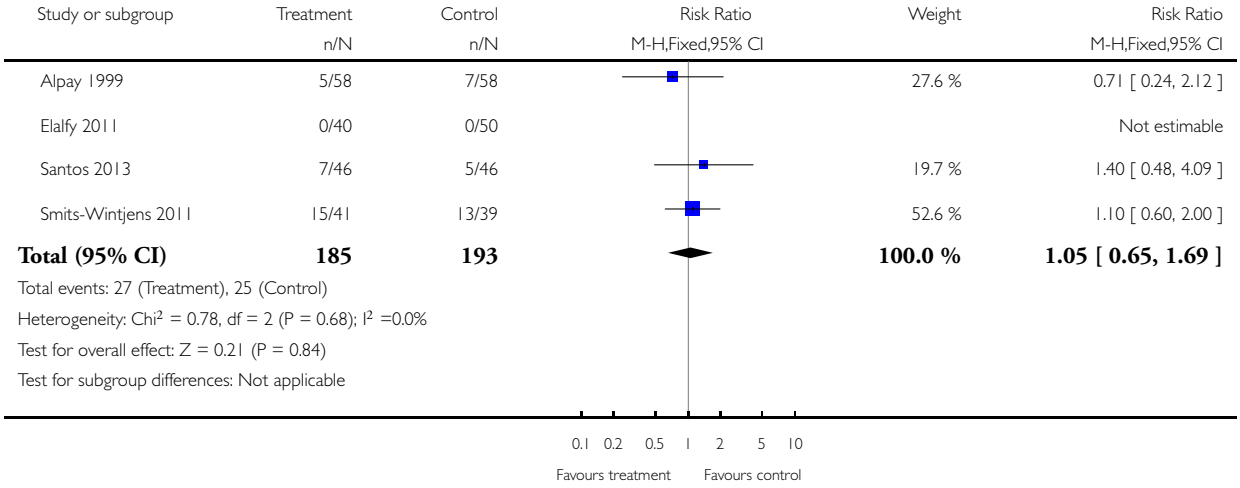


Analysis 4.3. Comparison 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg, Outcome 3 Use of top-up transfusions in 1st week.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg

Outcome: 3 Use of top-up transfusions in 1st week



Analysis 4.4. Comparison 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg, Outcome 4 Top-up transfusions in 1st week per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg

Outcome: 4 Top-up transfusions in 1st week per infant

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Elalfy 2011	40	0 (0)	50	0 (0)			Not estimable
Santos 2013	46	0.15 (0.36)	46	0.11 (0.32)		74.1 %	0.04 [-0.10, 0.18]
Smits-Wintjens 2011	41	0.41 (0.59)	39	0.33 (0.48)		25.9 %	0.08 [-0.16, 0.32]
Total (95% CI)	**127**		**135**			**100.0 %**	**0.05 [-0.07, 0.17]**

Heterogeneity: $Chi^2 = 0.08$, df = 1 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable

Analysis 4.5. Comparison 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg, Outcome 5 Use of top-up transfusion after 1st week.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg

Outcome: 5 Use of top-up transfusion after 1st week

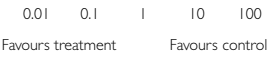
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alpay 1999	5/58	0/58		0.9 %	11.00 [0.62, 194.49]
Dağ oğ lu 1995	22/22	19/19		35.6 %	1.00 [0.91, 1.10]
Miqdad 2004	0/56	0/56			Not estimable
Rübo 1992	2/16	0/16		0.9 %	5.00 [0.26, 96.59]
Santos 2013	4/46	4/46		6.8 %	1.00 [0.27, 3.76]
Smits-Wintjens 2011	34/41	32/39		55.9 %	1.01 [0.83, 1.24]
Total (95% CI)	**239**	**234**		**100.0 %**	**1.13 [0.95, 1.33]**

Total events: 67 (Treatment), 55 (Control)

Heterogeneity: Chi^2 = 10.71, df = 4 (P = 0.03); I^2 =63%

Test for overall effect: Z = 1.37 (P = 0.17)

Test for subgroup differences: Not applicable



Analysis 4.6. Comparison 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg, Outcome 6 Top-up transfusions after 1st week per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg

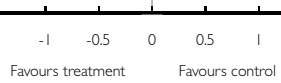
Outcome: 6 Top-up transfusions after 1st week per infant

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Miqdad 2004	56	0 (0)	56	0 (0)			Not estimable
Rübo 1992	16	0.19 (0.54)	16	0 (0)			Not estimable
Santos 2013	46	0.09 (0.29)	46	0.09 (0.29)		96.0 %	0.0 [-0.12, 0.12]
Smits-Wintjens 2011	41	1.83 (1.32)	39	1.85 (1.33)		4.0 %	-0.02 [-0.60, 0.56]
Total (95% CI)	**159**		**157**			**100.0 %**	**0.00 [-0.12, 0.12]**

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable

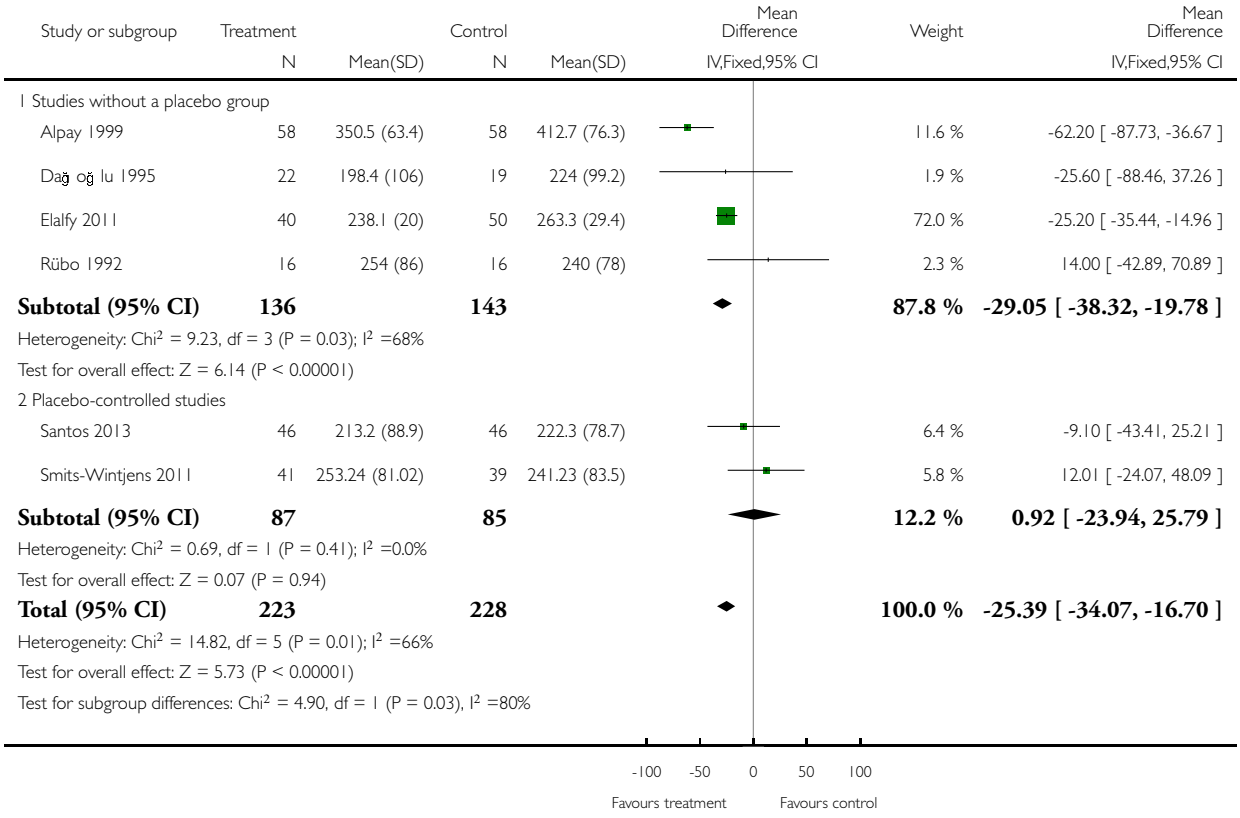


Analysis 4.7. Comparison 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg, Outcome 7 Maximum total serum bilirubin (µmol/L).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg

Outcome: 7 Maximum total serum bilirubin (mol/L)

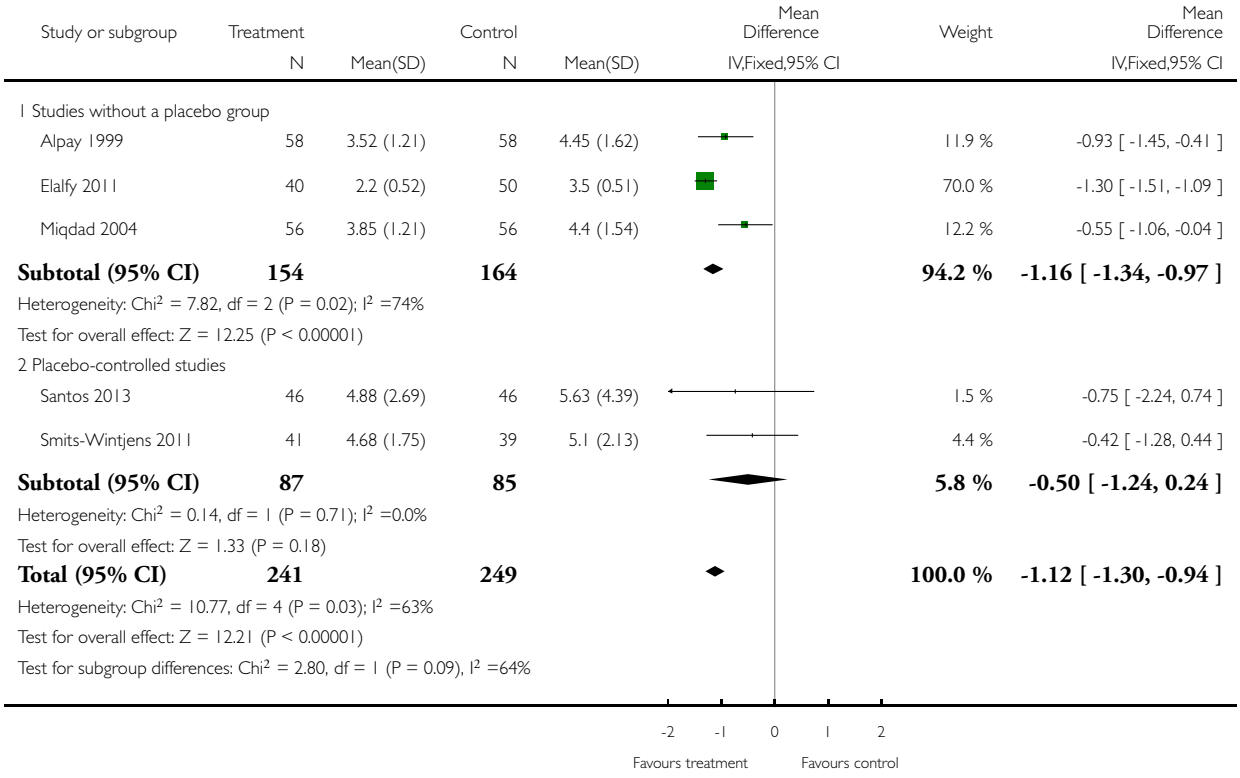


Analysis 4.8. Comparison 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg, Outcome 8 Duration of phototherapy (days).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 4 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Single dose of IVIg

Outcome: 8 Duration of phototherapy (days)



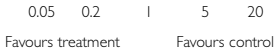
Analysis 5.1. Comparison 5 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Multiple doses of IVIg, Outcome 1 Use of exchange transfusion (≥ 1).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 5 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Multiple doses of IVIg

Outcome: 1 Use of exchange transfusion (≥ 1)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nasseri 2006	3/17	11/17		100.0 %	0.27 [0.09, 0.81]
Total (95% CI)	**17**	**17**		**100.0 %**	**0.27 [0.09, 0.81]**
Total events: 3 (Treatment), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.35 (P = 0.019)					
Test for subgroup differences: Not applicable					



Analysis 5.2. Comparison 5 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Multiple doses of IVIg, Outcome 2 Exchange transfusions per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 5 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Multiple doses of IVIg

Outcome: 2 Exchange transfusions per infant

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Nasseri 2006	17	0.17 (0.39)	17	1.11 (0.99)		100.0 %	-0.94 [-1.45, -0.43]
Total (95% CI)	**17**		**17**			**100.0 %**	**-0.94 [-1.45, -0.43]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.64 (P = 0.00027)							
Test for subgroup differences: Not applicable							

Analysis 5.3. Comparison 5 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Multiple doses of IVIg, Outcome 3 Use of top-up transfusions after 1st week.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 5 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Multiple doses of IVIg

Outcome: 3 Use of top-up transfusions after 1st week

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Nasseri 2006	2/17	0/17		100.0 %	5.65 [0.25, 126.87]
Total (95% CI)	**17**	**17**		**100.0 %**	**5.65 [0.25, 126.87]**
Total events: 2 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.09 (P = 0.28)					
Test for subgroup differences: Not applicable					

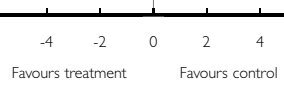
Analysis 5.4. Comparison 5 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Multiple doses of IVIg, Outcome 4 Duration of phototherapy (days).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 5 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Multiple doses of IVIg

Outcome: 4 Duration of phototherapy (days)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Nasseri 2006	17	4.94 (0.96)	17	6.41 (2)		100.0 %	-1.47 [-2.52, -0.42]
Total (95% CI)	**17**		**17**			**100.0 %**	**-1.47 [-2.52, -0.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.73 (P = 0.0063)							
Test for subgroup differences: Not applicable							

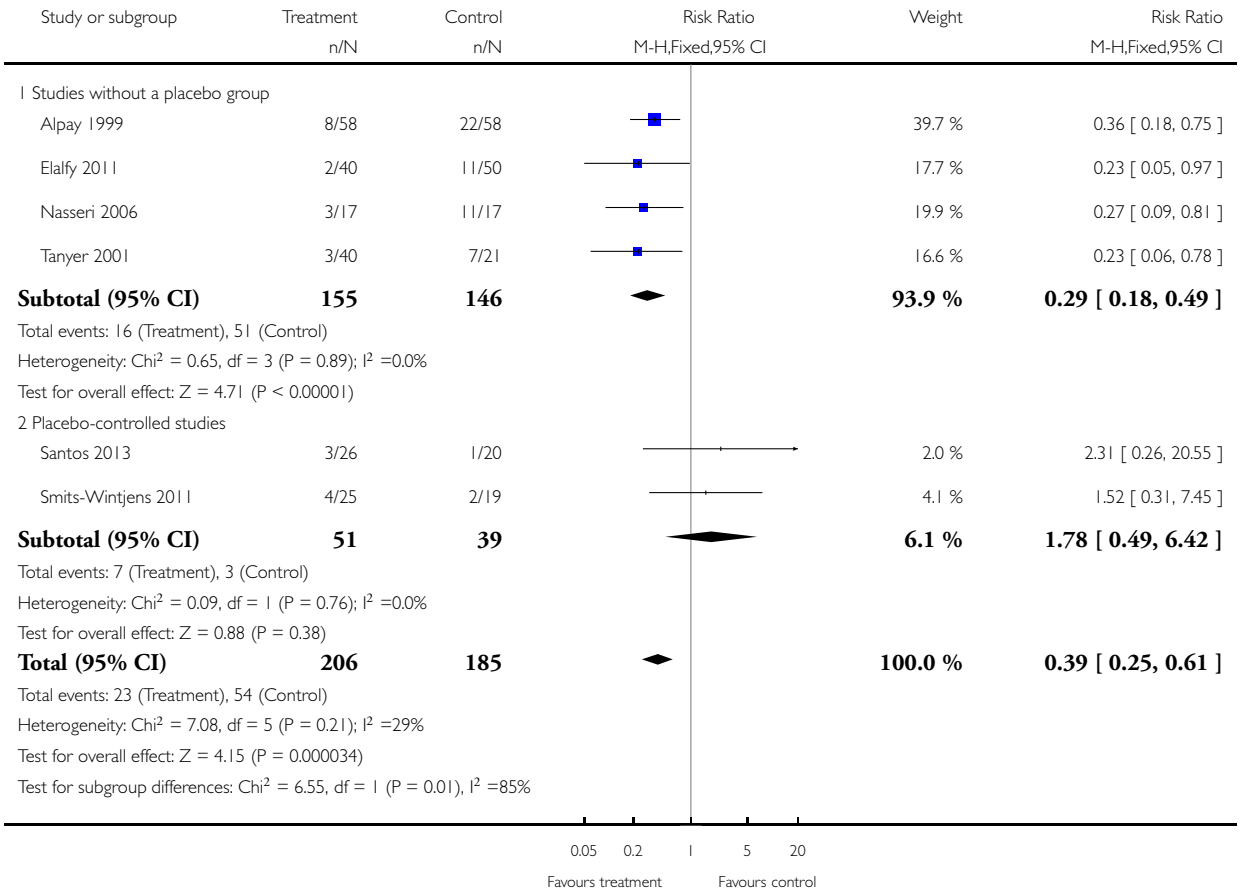


Analysis 6.1. Comparison 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks, Outcome 1 Use of exchange transfusion (≥ 1).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

Outcome: 1 Use of exchange transfusion (≥ 1)

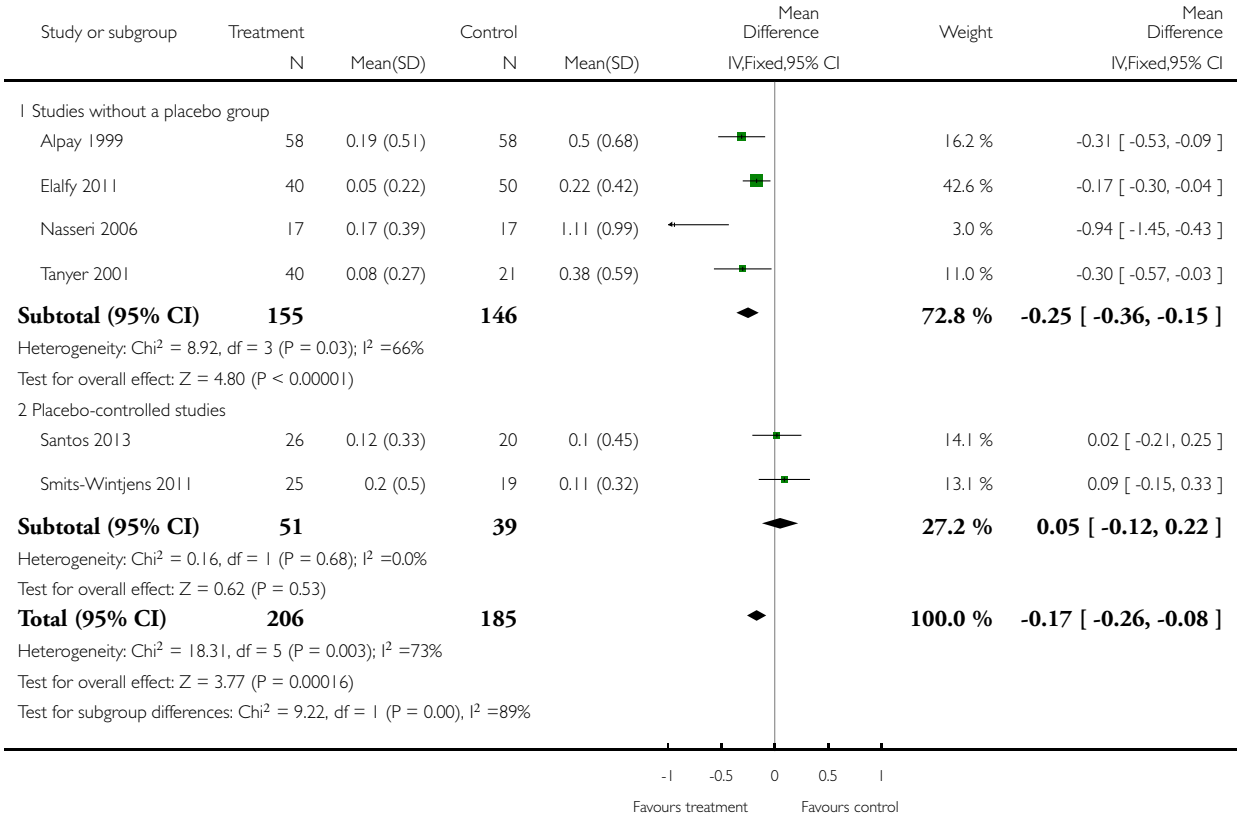


Analysis 6.2. Comparison 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks, Outcome 2 Exchange transfusions per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

Outcome: 2 Exchange transfusions per infant



Analysis 6.3. Comparison 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks, Outcome 3 Use of top-up transfusion in 1st week.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

Outcome: 3 Use of top-up transfusion in 1st week

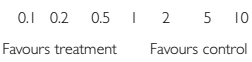
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alpay 1999	5/58	7/58		45.1 %	0.71 [0.24, 2.12]
Elalfy 2011	0/40	0/50			Not estimable
Santos 2013	3/26	0/20		3.6 %	5.44 [0.30, 99.72]
Smits-Wintjens 2011	7/25	7/19		51.3 %	0.76 [0.32, 1.80]
Total (95% CI)	**149**	**147**		**100.0 %**	**0.91 [0.48, 1.74]**

Total events: 15 (Treatment), 14 (Control)

Heterogeneity: $Chi^2 = 1.81$, df = 2 (P = 0.40); $I^2 = 0.0\%$

Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks, Outcome 4 Top-up transfusions in 1st week per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

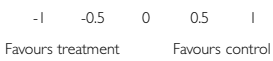
Outcome: 4 Top-up transfusions in 1st week per infant

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Elalfy 2011	40	0 (0)	50	0 (0)			Not estimable
Santos 2013	26	0.12 (0.33)	20	0 (0)			Not estimable
Smits-Wintjens 2011	25	0.36 (0.64)	19	0.37 (0.5)		100.0 %	-0.01 [-0.35, 0.33]
Total (95% CI)	**91**		**89**			**100.0 %**	**-0.01 [-0.35, 0.33]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.06 (P = 0.95)

Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks, Outcome 5 Use of top-up transfusion after 1st week.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

Outcome: 5 Use of top-up transfusion after 1st week

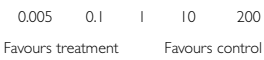
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alpay 1999	5/58	0/58		2.3 %	11.00 [0.62, 194.49]
Nasseri 2006	2/17	0/17		2.3 %	5.00 [0.26, 97.00]
Santos 2013	2/26	2/20		10.5 %	0.77 [0.12, 5.00]
Smits-Wintjens 2011	18/25	16/19		84.8 %	0.86 [0.63, 1.17]
Total (95% CI)	**126**	**114**		**100.0 %**	**1.18 [0.81, 1.71]**

Total events: 27 (Treatment), 18 (Control)

Heterogeneity: Chi^2 = 7.50, df = 3 (P = 0.06); I^2 =60%

Test for overall effect: Z = 0.87 (P = 0.39)

Test for subgroup differences: Not applicable



Analysis 6.6. Comparison 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks, Outcome 6 Top-up transfusions after 1st week per infant.

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

Outcome: 6 Top-up transfusions after 1st week per infant

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Santos 2013	26	0.08 (0.27)	20	0.1 (0.31)		95.8 %	-0.02 [-0.19, 0.15]
Smits-Wintjens 2011	25	1.6 (1.35)	19	1.95 (1.39)		4.2 %	-0.35 [-1.17, 0.47]
Total (95% CI)	**51**		**39**			**100.0 %**	**-0.03 [-0.20, 0.13]**

Heterogeneity: Chi^2 = 0.60, df = 1 (P = 0.44); I^2 =0.0%

Test for overall effect: Z = 0.40 (P = 0.69)

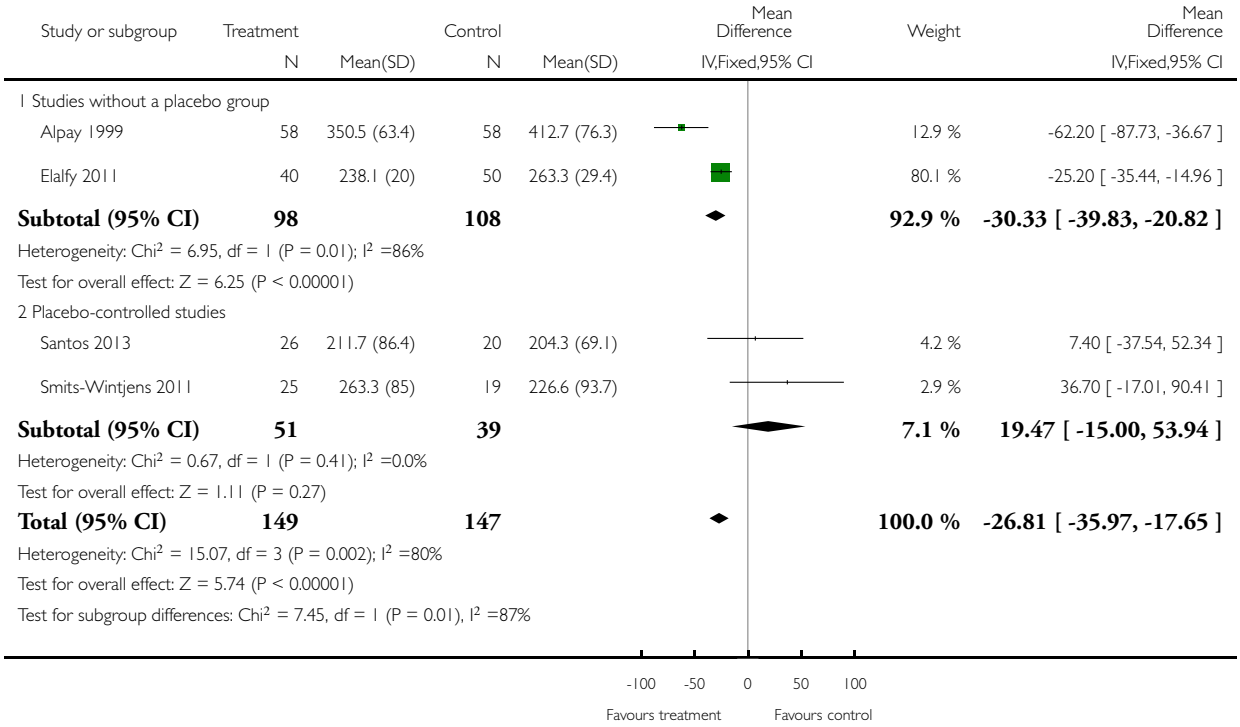
Test for subgroup differences: Not applicable

Analysis 6.7. Comparison 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks, Outcome 7 Maximum total serum bilirubin (µmol/L).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

Outcome: 7 Maximum total serum bilirubin (mol/L)



Analysis 6.8. Comparison 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks, Outcome 8 Duration of phototherapy (days).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

Outcome: 8 Duration of phototherapy (days)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Studies without a placebo group							
Alpay 1999	58	3.52 (1.21)	58	4.45 (1.62)		12.9 %	-0.93 [-1.45, -0.41]
Elalfy 2011	40	2.2 (0.52)	50	3.5 (0.51)		76.0 %	-1.30 [-1.51, -1.09]
Nasseri 2006	17	4.94 (0.96)	17	6.41 (2)		3.1 %	-1.47 [-2.52, -0.42]
Tanyer 2001	40	3.25 (1.75)	21	4.5 (1.8)		3.9 %	-1.25 [-2.19, -0.31]
Subtotal (95% CI)	**155**		**146**			**96.0 %**	**-1.25 [-1.44, -1.06]**
Heterogeneity: Chi² = 1.83, df = 3 (P = 0.61); I² =0.0%							
Test for overall effect: Z = 12.88 (P < 0.00001)							
2 Placebo-controlled studies							
Santos 2013	26	4.66 (1.99)	20	4.1 (2.63)		1.8 %	0.56 [-0.82, 1.94]
Smits-Wintjens 2011	25	4.76 (1.9)	19	4.89 (2.28)		2.2 %	-0.13 [-1.40, 1.14]
Subtotal (95% CI)	**51**		**39**			**4.0 %**	**0.18 [-0.75, 1.12]**
Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² =0.0%							
Test for overall effect: Z = 0.39 (P = 0.70)							
Total (95% CI)	**206**		**185**			**100.0 %**	**-1.20 [-1.38, -1.01]**
Heterogeneity: Chi² = 11.09, df = 5 (P = 0.05); I² =55%							
Test for overall effect: Z = 12.54 (P < 0.00001)							
Test for subgroup differences: Chi² = 8.74, df = 1 (P = 0.00), I² =89%							

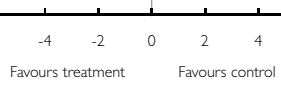
Analysis 6.9. Comparison 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks, Outcome 9 Duration of hospitalization (days).

Review: Immunoglobulin for alloimmune hemolytic disease in neonates

Comparison: 6 Intravenous immunoglobulin (IVIg) plus phototherapy versus phototherapy. Gestational age ≥ 37 weeks

Outcome: 9 Duration of hospitalization (days)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Studies without a placebo group							
Alpay 1999	58	4.52 (1.43)	58	5.5 (1.81)		19.3 %	-0.98 [-1.57, -0.39]
Elalfy 2011	40	3.25 (0.71)	50	4.72 (0.78)		71.5 %	-1.47 [-1.78, -1.16]
Nasseri 2006	17	6 (1)	17	7.41 (2.09)		5.6 %	-1.41 [-2.51, -0.31]
Subtotal (95% CI)	**115**		**125**			**96.4 %**	**-1.37 [-1.63, -1.10]**
Heterogeneity: Chi^2 = 2.07, df = 2 (P = 0.36); I^2 =3%							
Test for overall effect: Z = 10.10 (P < 0.00001)							
2 Placebo-controlled studies							
Santos 2013	26	6.68 (2.43)	20	7.1 (3.25)		2.3 %	-0.42 [-2.12, 1.28]
Smits-Wintjens 2011	25	7.28 (4.62)	19	7.42 (3.13)		1.3 %	-0.14 [-2.43, 2.15]
Subtotal (95% CI)	**51**		**39**			**3.6 %**	**-0.32 [-1.69, 1.05]**
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.85); I^2 =0.0%							
Test for overall effect: Z = 0.46 (P = 0.65)							
Total (95% CI)	**166**		**164**			**100.0 %**	**-1.33 [-1.59, -1.07]**
Heterogeneity: Chi^2 = 4.28, df = 4 (P = 0.37); I^2 =6%							
Test for overall effect: Z = 10.00 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.17, df = 1 (P = 0.14), I^2 =54%							



APPENDICES

Appendix 1. Complete search strategy

Database	Search strategy	Number of unique references
PubMed	Strategy 1: limited to RCTs or Systematic Reviews (immunoglobulin OR gammaglobulin or immunoglobulins OR gammaglobulins OR "Immunoglobulins"[Mesh] OR "Immunoglobulins, Intravenous"[mesh] OR "Intravenous Immune Globulin" OR "Intravenous Immune Globulins" OR IVIG OR "Intravenous IG" OR "Intravenous Immunoglobulins" OR "Intravenous Immunoglobulin" OR "IV Immunoglobulins" OR "Intravenous Antibodies" OR "Intravenous Antibody" OR "Venoglobulin-I" OR "Venoglobulin I" OR VenoglobulinI OR Gamimune OR Gamimmune OR "Gamimune N" OR "Gamimmune N" OR Gammagard OR Gammonativ OR "Globulin-N" OR "Globulin N" OR GlobulinN OR Intraglobin OR Iveegam OR "Modified Immune Globulin" OR Sandoglobulin OR Venimmune OR Venoglobulin OR Alphaglobin OR Endobulin) AND (((isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR jaundice OR hyperbilirubinemia OR hyperbilirubinemi* OR haemolysis OR haemolytic OR haemolytic OR haemolysis OR hyperbilirubinemia OR hyperbilirubinaemi* OR rhesus OR isoimmune OR "Anemia, Hemolytic"[mesh] OR "Jaundice"[mesh] OR "Hyperbilirubinemia"[mesh] OR "Hemolysis"[mesh]) AND ("Infant, Newborn"[mesh] OR newborn OR newborns OR neon* OR neonate OR neonates OR neonat* OR neonatal OR "Low Birth Weight Infant" OR "Small for Gestational Age Infant" OR "Very Low Birth Weight Infant" OR "Postmature Infant" OR "Premature Infant" OR "Low Birth Weight Infants" OR "Small for Ges-	873

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	tational Age Infants" OR "Very Low Birth Weight Infants" OR "Postmature Infants" OR "Premature Infants" OR premature OR low birth weight OR VLBW OR LBW)) OR "Anemia, Neonatal" OR "Jaundice, Neonatal") AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti] OR RCT OR RCTS OR randomized [tiab] OR systematic[sb]) Strategy 2: focus on Immunoglobulin infusion and isoimmune haemolytic jaundice, no other limits applied immunoglobulin[ti] OR gammaglobulin[ti] or immunoglobulins[ti] OR gammaglobulins[ti] OR "Immunoglobulins"[majr] OR "Immunoglobulins, Intravenous"[majr] OR "Intravenous Immune Globulin"[ti] OR "Intravenous Immune Globulins"[ti] OR IVIG[ti] OR "Intravenous IG"[ti] OR "Intravenous Immunoglobulins"[ti] OR "Intravenous Immunoglobulin"[ti] OR "IV Immunoglobulins"[ti] OR (Intravenous[ti] AND Antibodies[ti]) OR "Intravenous Antibody"[ti] OR "Venoglobulin-I"[ti] OR "Venoglobulin I"[ti] OR VenoglobulinI[ti] OR Gamimune[ti] OR Gamimmune[ti] OR "Gamimune N"[ti] OR "Gamimmune N"[ti] OR Gammagard[ti] OR Gammonativ[ti] OR "Globulin-N"[ti] OR "Globulin N"[ti] OR GlobulinN[ti] OR Intraglobin[ti] OR Iveegam[ti] OR "Modified Immune Globulin"[ti] OR Sandoglobulin[ti] OR Venimmune[ti] OR Venoglobulin[ti] OR Alphaglobin[ti] OR Endobulin[ti]) AND ((((isoimmune[ti] AND haemolytic[ti] AND jaundice[ti]) OR (alloimmune[ti] AND haemolytic[ti] AND jaundice[ti]) OR (isoimmune[ti] AND haemolytic[ti] AND jaundice[ti]) OR (alloimmune[ti] AND haemolytic[ti] AND jaundice[ti]) OR jaundice[ti] OR hyperbilirubinemia[ti] OR hyperbilirubinemi*[ti]	

(*Continued*)

	OR haemolysis[ti] OR haemolytic[ti] OR haemolytic[ti] OR haemolysis[ti] OR hyperbilirubinemia[ti] OR hyperbilirubinaemi*[ti] OR rhesus[ti] OR isoimmune[ti] OR "Anemia, Hemolytic"[majr] OR "Jaundice"[majr] OR "Hyperbilirubinemia"[majr] OR "Hemolysis"[majr]) AND ("Infant, Newborn"[mesh] OR newborn OR newborns OR neon* OR neonate OR neonates OR neonat* OR neonatal OR "Low Birth Weight Infant" OR "Small for Gestational Age Infant" OR "Very Low Birth Weight Infant" OR "Postmature Infant" OR "Premature Infant" OR "Low Birth Weight Infants" OR "Small for Gestational Age Infants" OR "Very Low Birth Weight Infants" OR "Postmature Infants" OR "Premature Infants" OR premature OR low birth weight OR VLBW OR LBW)) OR "Anemia, Neonatal" OR "Jaundice, Neonatal") NOT (animals [mh] NOT humans [mh])	
Embase (Ovid)	Strategy 1: limited to RCTs or Systematic Reviews (exp immunoglobulin/ OR (gammaglobulin* or immunoglobulin* OR "Immune Globulin*" OR IVIG OR "Intravenous IG" OR "Intravenous Antibod*" OR "Venoglobulin-I" OR "Venoglobulin I" OR VenoglobulinI OR Gamimune OR Gamimmune OR "Gamimune N" OR "Gamimmune N" OR Gammagard OR Gammonativ OR "Globulin-N" OR "Globulin N" OR GlobulinN OR Intraglobin OR Iveegam OR "Modified Immune Globulin" OR Sandoglobulin OR Venimmune OR Venoglobulin OR Alphaglobin OR Endobulin).mp) AND ((((isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR jaundice OR hyperbilirubinemia OR hyperbilirubinemi* OR haemolysis OR haemolytic OR haemolytic OR haemolysis OR hyperbilirubinemia OR hyperbilirubinaemi* OR rhesus OR isoimmune) .mp OR exp haemolytic anemia/ OR exp	530

(*Continued*)

	Jaundice/ OR exp hyperbilirubinemia/ OR exp haemolysis/) AND (exp Newborn/ OR (newborn OR newborns OR neon* OR neonate OR neonates OR neonat* OR neonatal OR "Low Birth Weight Infant" OR "Small for Gestational Age Infant" OR "Very Low Birth Weight Infant" OR "Postmature Infant" OR "Premature Infant" OR "Low Birth Weight Infants" OR "Small for Gestational Age Infants" OR "Very Low Birth Weight Infants" OR "Postmature Infants" OR "Premature Infants" OR premature OR low birth weight OR VLBW OR LBW).mp)) OR newborn jaundice/ or newborn anemia/) AND (exp randomised controlled trial/ OR exp controlled clinical trial/ OR random*.ti,ab OR placebo*.ti,ab OR exp "clinical trial (topic)"/ OR trial*.ti OR RCT.ti,ab OR RCTS.ti,ab OR exp evidence based medicine/) Strategy 2: focus on Immunoglobulin infusion and isoimmune haemolytic jaundice, no other limits applied (exp *immunoglobulin/ OR (gammaglobulin* OR immunoglobulin* OR "Immune Globulin*" OR IVIG OR "Intravenous IG" OR "Intravenous Antibod*" OR "Venoglobulin-I" OR "Venoglobulin I" OR VenoglobulinI OR Gamimune OR Gamimmune OR "Gamimune N" OR "Gamimmune N" OR Gammagard OR Gammonativ OR "Globulin-N" OR "Globulin N" OR GlobulinN OR Intraglobin OR Iveegam OR "Modified Immune Globulin" OR Sandoglobulin OR Venimmune OR Venoglobulin OR Alphaglobin OR Endobulin).ti) AND (((isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR jaundice OR hyperbilirubinemia OR hyperbilirubinemi* OR haemolysis OR haemolytic OR haemolytic OR haemolysis OR hyperbilirubinemia OR hyperbilirubinaemi* OR rhesus OR isoimmune).ti OR exp *haemolytic anemia/ OR exp *Jaundice/ OR exp *hyperbilirubinemia/ OR exp	

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	haemolysis/) AND (exp Newborn/ OR (newborn OR newborns OR neon OR neonate OR neonates OR neonat* OR neonatal OR "Low Birth Weight Infant" OR "Small for Gestational Age Infant" OR "Very Low Birth Weight Infant" OR "Postmature Infant" OR "Premature Infant" OR "Low Birth Weight Infants" OR "Small for Gestational Age Infants" OR "Very Low Birth Weight Infants" OR "Postmature Infants" OR "Premature Infants" OR premature OR low birth weight OR VLBW OR LBW).mp)) OR *newborn jaundice/ or *newborn anemia/) AND exp human/	
The Cochrane Library (including CENTRAL)	(immunoglobulin OR gammaglobulin or immunoglobulins OR gammaglobulins OR Intravenous Immune Globulin OR Intravenous Immune Globulins OR IVIG OR Intravenous IG OR Intravenous Immunoglobulins OR Intravenous Immunoglobulin OR IV Immunoglobulins OR Intravenous Antibodies OR Intravenous Antibody OR Venoglobulin-I OR Venoglobulin I OR VenoglobulinI OR Gamimune OR Gamimmune OR Gamimune N OR Gamimmune N OR Gammagard OR Gammonativ OR Globulin-N OR Globulin N OR GlobulinN OR Intraglobin OR Iveegam OR Modified Immune Globulin OR Sandoglobulin OR Venimmune OR Venoglobulin OR Alphaglobin OR Endobulin) AND (isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR jaundice OR hyperbilirubinemia OR hyperbilirubinemi* OR haemolysis OR haemolytic OR haemolytic OR haemolysis OR hyperbilirubinemia OR hyperbilirubinaemi* OR rhesus OR isoimmune) AND (newborn OR newborns OR neon* OR neonate OR neonates OR neonat* OR neonatal OR Low Birth Weight Infant OR Small for Gestational Age Infant OR Very Low Birth Weight Infant OR Postmature Infant OR Premature Infant OR Low Birth Weight Infants OR Small for Gestational Age In-	19

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	fants OR Very Low Birth Weight Infants OR Postmature Infants OR Premature Infants OR premature OR low birth weight OR VLBW OR LBW)	
Web of Science	TS=((immunoglobulin OR gammaglobulin or immunoglobulins OR gammaglobulins OR Intravenous Immune Globulin OR Intravenous Immune Globulins OR IVIG OR Intravenous IG OR Intravenous Immunoglobulins OR Intravenous Immunoglobulin OR IV Immunoglobulins OR Intravenous Antibodies OR Intravenous Antibody OR Venoglobulin-I OR Venoglobulin I OR VenoglobulinI OR Gamimune OR Gamimmune OR Gamimune N OR Gamimmune N OR Gammagard OR Gammonativ OR Globulin-N OR Globulin N OR GlobulinN OR Intraglobin OR Iveegam OR Modified Immune Globulin OR Sandoglobulin OR Venimmune OR Venoglobulin OR Alphaglobin OR Endobulin) AND (isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR jaundice OR hyperbilirubinemia OR hyperbilirubinemi* OR haemolysis OR haemolytic OR haemolytic OR haemolysis OR hyperbilirubinemia OR hyperbilirubinaemi* OR rhesus OR isoimmune) AND (newborn OR newborns OR neon* OR neonate OR neonates OR neonat* OR neonatal OR Low Birth Weight Infant OR Small for Gestational Age Infant OR Very Low Birth Weight Infant OR Postmature Infant OR Premature Infant OR Low Birth Weight Infants OR Small for Gestational Age Infants OR Very Low Birth Weight Infants OR Postmature Infants OR Premature Infants OR premature OR low birth weight OR VLBW OR LBW) AND (trial* OR RCT* OR random* OR placebo* OR eviden* OR systematic*))	68
CINAHL (EBSCOhost), replaced by Emcare per 1 January 2017	((immunoglobulin OR gammaglobulin or immunoglobulins OR gammaglobulins OR Intravenous Immune Globulin	45

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	OR Intravenous Immune Globulins OR IVIG OR Intravenous IG OR Intravenous Immunoglobulins OR Intravenous Immunoglobulin OR IV Immunoglobulins OR Intravenous Antibodies OR Intravenous Antibody OR Venoglobulin-I OR Venoglobulin I OR VenoglobulinI OR Gamimune OR Gamimmune OR Gamimune N OR Gamimmune N OR Gammagard OR Gammonativ OR Globulin-N OR Globulin N OR GlobulinN OR Intraglobin OR Iveegam OR Modified Immune Globulin OR Sandoglobulin OR Venimmune OR Venoglobulin OR Alphaglobin OR Endobulin) AND (isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR jaundice OR hyperbilirubinemia OR hyperbilirubinemi* OR haemolysis OR haemolytic OR haemolytic OR haemolysis OR hyperbilirubinemia OR hyperbilirubinaemi* OR rhesus OR isoimmune) AND (newborn OR newborns OR neon* OR neonate OR neonates OR neonat* OR neonatal OR Low Birth Weight Infant OR Small for Gestational Age Infant OR Very Low Birth Weight Infant OR Postmature Infant OR Premature Infant OR Low Birth Weight Infants OR Small for Gestational Age Infants OR Very Low Birth Weight Infants OR Postmature Infants OR Premature Infants OR premature OR low birth weight OR VLBW OR LBW))	
Academic Search Premier	((immunoglobulin OR gammaglobulin or immunoglobulins OR gammaglobulins OR Intravenous Immune Globulin OR Intravenous Immune Globulins OR IVIG OR Intravenous IG OR Intravenous Immunoglobulins OR Intravenous Immunoglobulin OR IV Immunoglobulins OR Intravenous Antibodies OR Intravenous Antibody OR Venoglobulin-I OR Venoglobulin I OR VenoglobulinI OR Gamimune OR Gamimmune OR Gamimune N OR Gamimmune N OR Gammagard OR Gammonativ OR Glob-	30

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	ulin-N OR Globulin N OR GlobulinN OR Intraglobin OR Iveegam OR Modified Immune Globulin OR Sandoglobulin OR Venimmune OR Venoglobulin OR Alphaglobin OR Endobulin) AND (isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR jaundice OR hyperbilirubinemia OR hyperbilirubinemi* OR haemolysis OR haemolytic OR haemolytic OR haemolysis OR hyperbilirubinemia OR hyperbilirubinaemi* OR rhesus OR isoimmune) AND (newborn OR newborns OR neon* OR neonate OR neonates OR neonat* OR neonatal OR Low Birth Weight Infant OR Small for Gestational Age Infant OR Very Low Birth Weight Infant OR Postmature Infant OR Premature Infant OR Low Birth Weight Infants OR Small for Gestational Age Infants OR Very Low Birth Weight Infants OR Postmature Infants OR Premature Infants OR premature OR low birth weight OR VLBW OR LBW))	
Emcare	Strategy 1: limited to RCTs or Systematic Reviews (exp immunoglobulin/ OR (gammaglobulin* or immunoglobulin* OR "Immune Globulin*" OR IVIG OR "Intravenous IG" OR "Intravenous Antibod*" OR "Venoglobulin-I" OR "Venoglobulin I" OR VenoglobulinI OR Gamimune OR Gamimmune OR "Gamimune N" OR "Gamimmune N" OR Gammagard OR Gammonativ OR "Globulin-N" OR "Globulin N" OR GlobulinN OR Intraglobin OR Iveegam OR "Modified Immune Globulin" OR Sandoglobulin OR Venimmune OR Venoglobulin OR Alphaglobin OR Endobulin).mp) AND ((((isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR jaundice OR hyperbilirubinaemia OR hyperbilirubinemi* OR haemolysis OR haemolytic OR haemolytic OR haemol-	0

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	ysis OR hyperbilirubinemia OR hyperbilirubinaemi* OR rhesus OR isoimmune) .mp OR exp haemolytic anemia/ OR exp Jaundice/ OR exp hyperbilirubinemia/ OR exp haemolysis/) AND (exp Newborn/ OR (newborn OR newborns OR neon* OR neonate OR neonates OR neonat* OR neonatal OR "Low Birth Weight Infant" OR "Small for Gestational Age Infant" OR "Very Low Birth Weight Infant" OR "Postmature Infant" OR "Premature Infant" OR "Low Birth Weight Infants" OR "Small for Gestational Age Infants" OR "Very Low Birth Weight Infants" OR "Postmature Infants" OR "Premature Infants" OR premature OR low birth weight OR VLBW OR LBW).mp)) OR newborn jaundice/ or newborn anemia/) AND (exp randomised controlled trial/ OR exp controlled clinical trial/ OR random*.ti,ab OR placebo*.ti,ab OR exp "clinical trial (topic)"/ OR trial*.ti OR RCT.ti,ab OR RCTS.ti,ab OR exp evidence based medicine/) Strategy 2: focus on Immunoglobulin infusion and isoimmune haemolytic jaundice, no other limits applied (exp *immunoglobulin/ OR (gammaglobulin* OR immunoglobulin* OR "Immune Globulin*" OR IVIG OR "Intravenous IG" OR "Intravenous Antibod*" OR "Venoglobulin-I" OR "Venoglobulin I" OR VenoglobulinI OR Gamimune OR Gamimmune OR "Gamimune N" OR "Gamimmune N" OR Gammagard OR Gammonativ OR "Globulin-N" OR "Globulin N" OR GlobulinN OR Intraglobin OR Iveegam OR "Modified Immune Globulin" OR Sandoglobulin OR Venimmune OR Venoglobulin OR Alphaglobin OR Endobulin).ti) AND ((((isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR isoimmune haemolytic jaundice OR alloimmune haemolytic jaundice OR jaundice OR hyperbilirubinemia OR hyperbilirubinemi* OR haemolysis OR haemolytic OR haemolytic OR haemolysis OR hyperbilirubinemia OR hyperbilirubi-	

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	naemi* OR rhesus OR isoimmune).ti OR exp *haemolytic anemia/ OR exp *Jaundice/ OR exp *hyperbilirubinemia/ OR exp *haemolysis/) AND (exp Newborn/ OR (newborn OR newborns OR neon* OR neonate OR neonates OR neonat* OR neonatal OR "Low Birth Weight Infant" OR "Small for Gestational Age Infant" OR "Very Low Birth Weight Infant" OR "Postmature Infant" OR "Premature Infant" OR "Low Birth Weight Infants" OR "Small for Gestational Age Infants" OR "Very Low Birth Weight Infants" OR "Postmature Infants" OR "Premature Infants" OR premature OR low birth weight OR VLBW OR LBW).mp)) OR *newborn jaundice/ or *newborn anemia/) AND exp human/	
Total		1565

WHAT'S NEW

Last assessed as up-to-date: 19 May 2017.

Date	Event	Description
16 October 2017	New citation required but conclusions have not changed	We updated the searches in May 2017 and found two new studies for inclusion; however, the conclusions were unchanged
16 October 2017	New search has been performed	In this version, we updated the existing (2002) review as follows: We updated the search and included seven new studies. We updated the background to include contemporary literature. Eligible participants were specified more precisely as neonates who had from Rh or ABO hemolytic disease and the primary and secondary outcome results were adjusted accordingly. Previously, the subgroup analysis for timing of intravenous immunoglobulin (IVIg) treatment was divided into 'prophylactic use' and 'treatment of established jaundice.' For the current review, this was changed to within 12 hours of birth or later, because the treatment intention was only by inference. A sensitivity analysis for risk of performance or detection bias (or both) was added. Furthermore, we incorporated a GRADE assessment of

(*Continued*)

		level of evidence and added a 'Summary of findings' table for the most important outcomes

HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 3, 2002

Date	Event	Description
19 August 2015	New search has been performed	This updates the review 'Immunoglobulin for alloimmune hemolytic disease in neonates' (Alcock 2002).
14 September 2012	New citation required but conclusions have not changed	New authorship. Updated search in March 2012 identified seven additional trials for inclusion in this review update
21 October 2008	Amended	Converted to new review format.
27 March 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Mirjam Rath wrote the protocol for the review. She also performed part of the literature search, assessed study methodology, extracted relevant data from included studies and contacted authors for any additional information required. She wrote a first version of the text of the review.

Carolien Zwiers updated the literature review, led the re-evaluation of included studies, and extensively revised all analyses and the text of the review, including updating of references in 'Background' and 'Discussion' sessions.

Helen Liley, Enrico Lopriore and Masja de Haas assisted in adapting the protocol and writing the review.

Helen Liley independently assessed study methodology and extracted data from included studies.

Enrico Lopriore was the third blinded review author.

Helen Liley and Carolien Zwiers performed the GRADE analysis of quality of evidence.

DECLARATIONS OF INTEREST

CZ: none.

MR: none.

EL: none.

MH: none.

HL: none.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In addition to analysis of all included studies, analyses were performed of all placebo-controlled studies. The search method, inclusion criteria and criteria to measure risk of bias were more extensively described in the review than in the protocol.

For the 2017 update, we updated the search and included seven new studies. We updated the background to include contemporary literature. The eligible participants were further specified (from "Neonates with isoimmune hemolytic disease" to "Neonates with alloimmune HDN due to either Rh or ABO blood group antibodies with or without any other blood group antibodies." The primary and secondary outcomes were adjusted to more relevant outcomes in the current era. Previously, the subgroup analysis for timing of IVIg treatment was divided in 'prophylactic use' and 'treatment of established jaundice'. For the current review, this was changed to within 12 hours of life or later. Due to the lack of definitions and the possibility of incomplete reporting in regard to adverse events, the adverse events of individual trials were stated in the current review, rather than combined raw outcomes of all included studies.

A sensitivity analysis for risk of performance or detection bias (or both) was added. Furthermore, we incorporated the GRADE criteria and added a 'Summary of findings' table for the most important outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Immunoglobulins, Intravenous; Anemia, Hemolytic [immunology; *therapy]; Anemia, Neonatal [immunology; *therapy]; Blood Transfusion; Jaundice, Neonatal [immunology; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn