

ORIGINAL ARTICLES

Administration of intravenous immunoglobulins for prophylaxis or treatment of infection in preterm infants: meta-analyses

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Abstract

Aims—To determine the effectiveness of intravenous immunoglobulin administration to premature infants in the prevention and/or treatment of bacterial infection.

Methods—Computer searches of MEDLINE, EMBASE, SCISEARCH and Oxford Database of Perinatal Trials were made. Two independent researchers applied inclusion criteria of: randomised controlled trial; premature and/or low birthweight infant; use of intravenous immunoglobulin; and infection or mortality. Nineteen of 44 identified studies fulfilled these criteria. Study quality was assessed and information on study population, intervention, and outcomes were collected.

Results—Studies were divided into prophylaxis or treatment; results were tabulated for infection, sepsis, and death from all causes. For 17 studies of prophylaxis (n=5245), the relative risk and confidence interval were, for proved infection 0.81, 0.67–0.97; for sepsis 0.87, 0.66–1.13; for death from all causes 0.85, 0.64–1.14. Some outcome results were heterogeneous. Two treatment studies showed no reduction in mortality when combined.

Conclusions—Routine administration of intravenous immunoglobulin to preterm infants is not recommended.

(*Arch Dis Child* 1995; 72: F151–F155)

Keywords: Intravenous immunoglobulin, infection, meta-analysis, preterm infants.

immunoglobulin (IVIG) administration to premature and/or low birthweight infants prevents nosocomial infections and/or improves outcomes in infants with suspected infections.

Several descriptive review articles of the use of immunoglobulins in neonates have been published. These have included several randomised controlled trials, the authors' personal experience with the drug, and/or information about the preparation or dosing regimen.^{2–5} Weisman *et al* combine the results of several randomised controlled trials using inappropriate statistical methods.⁶ Baley and Fanaroff presented overviews of randomised controlled trials on the administration of IVIG to neonates.⁷ They reviewed seven studies of the prophylactic use of IVIG which reported an outcome of sepsis, and three studies of the use of IVIG for treatment which reported an outcome of death. They concluded that: 'The preliminary data generated in trials of IVIG are promising, but use of this treatment modality still needs to be considered experimental and should only, as yet, be used under study conditions'. As many studies have been published since this review, a new critical overview of the use of IVIG in preterm infants is warranted.

Methods

We began the search with articles on this topic in our personal files and then searched the reference list of all these and subsequently retrieved articles. This search yielded 34 studies. MEDLINE was searched from 1966 onwards; we identified five additional studies. Next EMBASE (Excerpta Medica online) was searched from 1980. This search identified three additional studies. The Oxford Database of Perinatal Trials (Version 1.3, Disk Issue No 8, Autumn 1992) was also searched. No additional studies were identified. Two additional studies were identified from SCISEARCH (Science Citation Index). The titles (and abstracts when available) in the MEDLINE, EMBASE, and SCISEARCH printouts were reviewed by JBL and AO. Any article that either person felt might meet the inclusion criteria noted below or that either felt should have its reference list searched was retrieved. No attempt was made to locate unpublished studies. Although we are aware of publications bias,⁸ we felt that any search for

Although survival has improved for premature and/or low birthweight infants, congenital and nosocomial infection continue to be a significant cause of morbidity and mortality. Maternal transport of immunoglobulins to the fetus mainly occurs after 32 weeks' gestation and endogenous synthesis does not begin until about 24 weeks after birth, so premature infants are especially vulnerable to infection in the neonatal intensive care unit.¹ The administration of immunoglobulins to these infants has been studied extensively. The objective of this overview is to use meta-analytic techniques to determine if intravenous

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Accepted 7 February 1995

unpublished studies would result in considerable selection bias.

Criteria used to select studies for inclusion in this overview were:

(i) *Design*: randomised controlled trial with a control group that received a placebo or no intervention;

(ii) *Population*: premature (<37 weeks) and/or low birthweight (<2500 g) infants;

(iii) *Intervention*: IVIG;

(iv) *Outcome*: bacterial infection and/or mortality.

JBL and AO applied the above criteria separately and had 100% agreement. Sixteen studies published in full (14 for prophylaxis and two for treatment¹⁻⁹⁻²³) and three abstracts²⁴⁻²⁶ were accepted. Twenty five studies were rejected. (Log of rejected studies available on request from authors.)

An assessment of the quality of the included studies (excluding abstracts) was done independently by JBL and AO using the system developed by T C Chalmers.²⁷ This was not done with the assessors blinded to author, institution, journal of publication or results, as both assessors were familiar with most of the studies and the typographical layout of the journals, and would have had knowledge of these even with blinding; and results sections of articles often included methodological information. The Chalmers system uses 31 questions to assess the description of the study population and treatment, blinding, randomisation, statistical methods, withdrawals and side effects. The Fanaroff study had two

phases, the first of which was blinded¹⁵; quality of the study was assessed for each phase separately.

After the independent scoring the two assessors' total scores for each study were compared and yielded an intraclass correlation coefficient of 0.98.²⁸ The two assessors then together reviewed each question of the Chalmers system for each of the studies and by consensus developed an overall quality score. These consensus scores were used in the subsequent sensitivity analysis. Although it is possible to score 1.0 on the Chalmers system, in our experience most studies usually do not score above 0.8.²⁹⁻³⁰ A priori the decision was made to use 0.4 as the cutoff for an adequate quality score.

Data abstraction forms were developed and pilot tested to verify definitions of terms. JBL and AO independently abstracted information on each study and JBL checked for any discrepancies and pooled the results. Data abstraction included whether the study involved prophylaxis or treatment, the time period and geographical location of the study, baseline characteristics of patients, inclusion or exclusion criteria, preparation and dosing regimen of IVIG and placebo (table 1).

Information on outcomes and the numbers of affected infants was abstracted. Most studies reported on the total number of infants with proved infection (clinical signs and symptoms in conjunction with positive cultures from normally sterile body fluids). Many studies reported on sepsis (clinical signs and symptoms

Table 1 Study information

Author	Country	Prophylaxis/ treatment	Time period	Birthweight (g) T/C	Gestational age (week)	Intravenous immunoglobulin type/regimen	Placebo	Sample size T/C
Baker <i>et al</i> ¹	US	P	07/87-12/88	500-1750/ 500-1750	Not given	Gammagard 500 mg/kg 5 infusions: at entry, 1 week later, then every 14 days	5% albumin 0.9 NaCl	287/297
Brussel ⁹	US	P	09/84-10/87	977/1043	Not given	Sandoglobulin 1000 mg on 4 of first 5 days of life, fifth dose on day 15 to 21	Albumin	61/65
Chirico <i>et al</i> ¹⁰	Italy	P	01/83-07/85	1104/1157	29.7/29.9	Sandoglobulin 500 mg/kg weekly for 1 month	None	43/40
Christensen <i>et al</i> ¹¹	US	P	11/86-07/87	1130/1110	30.6/30.7	Gammune-N 750 mg/kg 1 infusion	0.1% albumin in 10% maltose	10/10
Clapp <i>et al</i> ¹²	US	P	11/86-08/87	1300/1300	30/31	Sandoglobulin serum IgG maintained at or near 700 mg/dl	6-10% sucrose	56/59
Conway <i>et al</i> ¹³	UK	P	Not given	1088/1043	27.5/27.5	Intraglobulin 200 mg/kg in first 48 hours, then every 3 weeks until discharge. If infection suspected: 100 mg/kg more. If proved, another 100 mg/kg	None	29/26
Didato <i>et al</i> ¹⁴	Italy	P	06/85-12/86	1438/1478	31/29	Gammaglobulin 500 mg/kg weekly until 36 weeks gestational age	None	40/40
Fanaroff <i>et al</i> ¹⁵	US	P	1/88-3/91	1082/1096	28.3/28.4	Sandoglobulin 900 mg/kg for birthweight <1000 g 700 mg/kg for birthweight 1000-1500 g, every 14 days until weight of 1.8 kg or discharge	Phase 1: albumin; phase 2: none	1204/1212
Haque <i>et al</i> ¹⁷	Saudi Arabia	P	Not given	1150/1100	32.4/33	Intraglobulin A: 120 mg/kg day 1; B: 120 mg/kg days 1, 8	None	100/50
Haque <i>et al</i> ¹⁶	Saudi Arabia	T	(6 months)	1320/1480	33.4/35	Pentaglobulin 190 mg/kg/day for 4 days	10% dextrose	30/30
Kacet <i>et al</i> ²⁴	France	P	Not given	1363/1354	30.2/30.3	500 mg/kg first day of life then weekly until 35 weeks	None	96/93
Magny <i>et al</i> ¹⁸	France	P	87-89	Not given	29.6/29.9	Polyvalent IgG 500 mg (10 ml) days 0, 1, 2, 3, 17, 31	0.2% albumin	120/115
Malik <i>et al</i> ²⁵	US	P	Not given	Not given	Not given	Sandoglobulin 500 mg/kg weekly for 4 months, 200 mg/kg for up to 6 months	None	15/15
Ratrisawadi <i>et al</i> ¹⁹	Thailand	P	02/88-03/90	1321/1290	31.3/31.0	Biotest Pharma Group 1: 250 mg/kg; Group 2: 500 mg/kg 1 infusion within 4 hours	None	68/34
Spady <i>et al</i> ²⁶	Canada	P	Not given	Not given	Not given	300 mg/kg at 24-72 hours of age and 72 hours later	5% dextrose	54/57
Stabile <i>et al</i> ²⁰	Italy	P	05/84-06/86	Not given	Not given	Venogamma Polivante 500 mg/kg on days 1, 2, 3, 7, 14, 21, 28	None	40/40
van Overmeire <i>et al</i> ²¹	Belgium	P	Not given	1150/1120	29.6/29.2	Sandoglobulin 500 mg/kg on days 1, 2, 3, 4, 5, 6, 7, 14, 21, 28	None	56/60
Weisman <i>et al</i> ²²	US	T	06/85-04/89	Not given	Not given	Sandoglobulin 500 mg/kg 1 infusion	Albumin 5% sucrose	14/17
Weisman <i>et al</i> ²³	US	P	06/85-04/89	1251/1251	29.6/29.5	Sandoglobulin 500 mg/kg 1 infusion	Albumin 5% sucrose	372/381

T=treatment; C=control; P=prophylaxis.

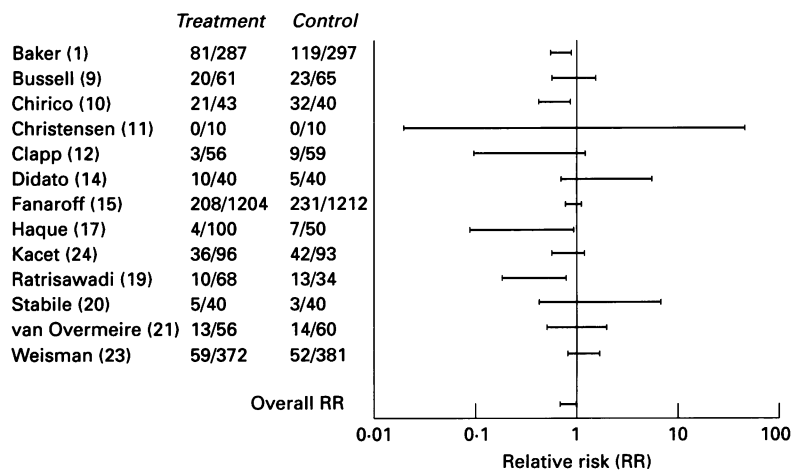


Figure 1 IVIG prophylaxis: effect on infection.

plus positive blood culture), necrotising enterocolitis, death from all causes, and deaths from infection. A few studies reported on length of hospital stay, ventilation, and incidence of bronchopulmonary dysplasia (BPD) and intra-ventricular haemorrhage (IVH).

STATISTICAL ANALYSIS

The Statistical Analysis System was used to calculate relative risk (RR) and 95% confidence intervals (CI). Due to substantial inter-study variability for the prophylactic use of IVIG, a random effects model was used.³¹ For the analysis of treatment with IVIG, a fixed effects model was used.³² To test for homogeneity, a Q-statistic was used for the random effects model and the Breslow-Day test was used for the fixed effects model.^{33 34} The primary analysis for the use of IVIG for prophylaxis included all 17 studies.^{1 9-15 17-21 23-26} A secondary analysis excluded studies with low quality score (<0.40) and studies that were published as abstracts (in which quality could not be assessed).^{10 13 17 19-21 24-26} The decision to analyse data in this manner was made a priori.

Results

PROPHYLAXIS

Figures 1 and 2 depict the individual study, outcome data, and typical RR for the outcomes

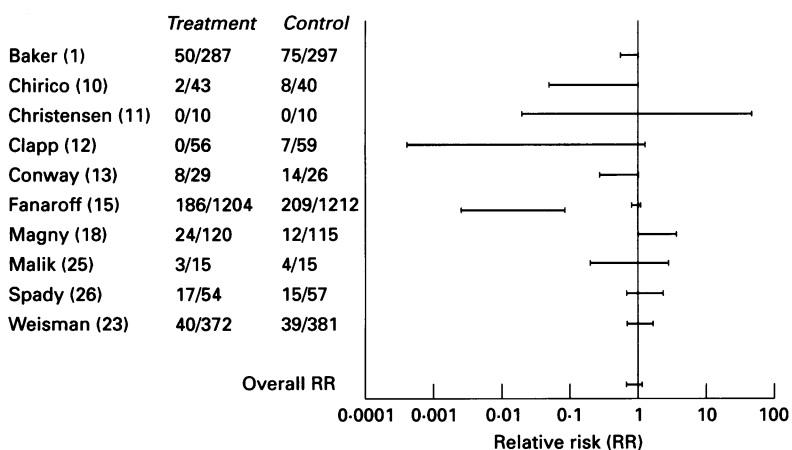


Figure 2 IVIG prophylaxis: effect on sepsis.

of proved infection and sepsis for all studies that reported those outcomes. Tables 2 and 3 list the RR and 95% CIs and the probability of the Q-statistic for homogeneity of the odds ratios for each of the five outcomes (proved infection, sepsis, necrotising enterocolitis, death from all causes, death from infection) of the two analyses.

When all the studies were included (table 2) for the outcome of proved infection, the RR of 0.81, CI 0.67-0.97 was significant. For all studies combined, there was no significant difference in sepsis, necrotising enterocolitis, death from all causes and death from infection.

The test from homogeneity indicated that the results for proved infection, sepsis, and necrotising enterocolitis across studies were heterogenous and according to this test, combining the results is inappropriate. When looking for differences among the studies (to explain the heterogeneity), we found that the birthweights and gestational ages of patients were essentially the same. Both placebo controlled and non placebo-controlled studies demonstrated positive results. Although the amount of IVIG varied from ≤ 200 mg/kg to 1000 mg/kg, and from one to more than four total doses, there were studies that demonstrated no benefit from IVIG and others that demonstrated benefit which used smaller or larger amounts and doses. Therefore, the population, intervention, and methodology of the studies were unlikely to be the cause of the heterogeneity of the results.

In the primary analyses in which there was heterogeneity for the results of proved infection, sepsis, and necrotising enterocolitis, there was homogeneity for the outcome results of death from all causes and death from infection. The variable way in which investigators measured the outcomes of proved infection, sepsis, and necrotising enterocolitis was probably responsible for the heterogeneity. When we examined the event rate of the various outcomes in the control groups of the studies in this overview we found an event rate for proved infection that ranged from 0 to 75% and an event rate for sepsis that ranged from 0 to 54%. The event rate for death from all causes was the least variable with a range of 4 to 33%. A high rate of proved infection or sepsis was generally not associated with a high rate of mortality.

In the secondary analyses (table 3) none of the outcomes was significantly reduced. These results for proved infection, necrotising enterocolitis, death from all causes and death from infection were homogenous; the results for sepsis were heterogenous.

Table 2 Summary of results of all studies for IVIG prophylaxis for neonatal infection^{1 9-15 17-21 23-26}

Outcome	Relative risk (95% CI)	Test for homogeneity
Proved infection	0.81 (0.67-0.97)	0.02
Sepsis	0.87 (0.66-1.13)	0.03
Necrotising enterocolitis	1.15 (0.80-1.64)	0.01
Death from all causes	0.85 (0.64-1.14)	0.28
Death from infection	1.11 (0.64-1.94)	0.42

Table 3 Summary of results for IVIG prophylaxis for neonatal infection^{1 9 11 12 14 15 18 23} excluding abstracts and low quality scores^{10 13 17 19–21 24–26}

Outcome	Relative risk (95% CI)	Test for homogeneity
Proved infection	0.90 (0.72–1.11)	0.08
Sepsis	0.94 (0.69–1.28)	0.04
Necrotising enterocolitis	1.13 (0.82–1.55)	0.05
Death from all causes	1.01 (0.82–1.23)	0.82
Death from infection	1.41 (0.73–2.72)	0.95

Other outcomes that were not found to be significantly different included: length of ventilation,^{1 10 13–15 18} incidence of BPD,^{1 10 13 15 23} and incidence of IVH.^{1 12 13 15 23} Many studies measured duration of hospital stay; however, as some reported on mean or median number of days in hospital and some reported on age at discharge, a meta-analysis of this outcome was not possible. Most studies found no difference in duration of hospital stay.^{1 10 12 15 21 24} Spady *et al* reported a significant reduction in mean age at discharge for a subgroup of infants who had sepsis in the treatment group compared with infants with sepsis in the control group.²⁶ Conway *et al* found a decrease in the median age at discharge for treated infants.¹³

TREATMENT

Only two studies used IVIG for treatment of infants with known infection. Both studies excluded randomly allocated infants with clinically suspected sepsis who later proved not to have positive cultures. Haque *et al* found no significant reduction in subsequent infection, but found a significant reduction in mortality.¹⁶ However, when combined with the results of the study by Weisman *et al*²² (who found no reduction in mortality), the RR was 0.38 (95% CI 0.12 to 1.19). The Breslow-Day test for homogeneity yielded a probability of 0.69, indicating that the results of this outcome were homogenous and could be combined.

SIDE EFFECTS

In most studies the investigators examined infants closely for possible side effects. Most side effects were transient and included hypotension, tachycardia, and haemolysis. These side effects were felt to be related to too rapid infusion of placebo or immunoglobulins. Spady *et al* noted a small but significant increase in respiratory rate following the first infusion of IVIG.²⁶

Discussion

Although the populations and interventions among the studies varied, we felt that there was enough similarity in the studies to make the cautious use of meta-analytic techniques appropriate. In the primary analysis of the prophylactic use of IVIG (inclusion of all studies), there was a reduction in proved infection, but not in the secondary analysis (exclusion of studies published only as abstracts or with poor quality scores). In the primary analysis the results were heterogenous; however, in the secondary analysis the results were homogenous.

When poor quality studies and abstracts were excluded, the effect size was reduced. Sepsis, necrotising enterocolitis, death from all causes or death from infection were not significantly reduced in either analyses. We found heterogeneity for many outcomes except mortality in either analysis, and proved infection and necrotising enterocolitis in the secondary analysis.

A reduction in proved infection in the primary analysis was not associated with a reduction in mortality. Using an event rate of 10% for overall mortality (which was the average event rate for control infants in this overview), a 25% risk of reduction, an α of 0.05, and a β of 0.80, a sample size of 4166 would be needed to show a significant reduction in mortality. The combined sample size for studies that reported on death from all causes in this review was 3837; therefore, the combined sample size did not have the power to detect a significant difference for this outcome.

Fanaroff *et al* have published the largest study on the prophylactic use of IVIG, with a total sample size of 2416 or 46% of the total sample size for all the studies of prophylaxis.¹⁵ Fanaroff *et al* conducted their study in two phases: phase 1 was blinded; phase 2 was unblinded. For both phases combined there was no overall reduction in proved infection, sepsis, or mortality. We calculated the relative risk separately for each phase of the study; for phase 1 there was a significant reduction in proved infection and sepsis in the treatment group; for phase 2 there was no significant reduction. We questioned whether the lack of blinding in the second phase resulted in biased measurement of the outcomes of proved infection and sepsis.³⁵ Fanaroff answered that our statistical analysis of the two phases separately had not accounted for multiple examination of the data and that we had therefore underestimated the width of the confidence interval, and that he felt that the possibility of bias in the latter half of the trial would have been more plausible if the trial had concluded that IVIG prevented nosocomial infections.³⁶

The studies in this review used a wide assortment of preparations of IVIG. Weisman *et al* studied a variety of commercial preparations of IVIG and concluded that 'pathogen-specific opsonic activity of an IVIG is highly variable for several common neonatal pathogens', and 'predominantly dependent on donor pool and not the manufacturing method'.³⁷ IVIG preparations used in the reviewed studies may not have contained the necessary antibodies to prevent or treat infection in the preterm infant. New preparations of IVIG with other antibodies or other combinations of antibodies might be effective.

Only two relatively small studies of the use of IVIG for treatment of infants with suspected infection have been published and when the studies were combined there was no reduction in mortality in infants with subsequently proved infection.^{16 22}

IVIG administration to preterm infants is not associated with serious side effects. Although we found a decreased RR for

proved infection in the primary analysis, we found no decrease in sepsis or mortality. We conclude that there is no clear evidence that the prophylactic use of IVIG, using current preparations, is beneficial for preterm infants. There is insubstantial evidence of a benefit of IVIG use for preterm infants who are already infected.

This project was supported by the Garfield Weston Foundation. We acknowledge the statistical assistance of Terri Myhr, MSc.

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