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Adjuvant use of intravenous immunoglobulin in the treatment of neonatal sepsis: a systematic review with a meta-analysis

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Abstract

Objective: To evaluate whether intravenous immunoglobulin reduces mortality and length of hospital stay in the treatment of neonatal sepsis.

Sources: The MEDLINE database was searched. The keywords were combined using the following search strategy: [(sepsis OR shock, septic OR infection) AND immunoglobulins, intravenous] AND infant, newborn. Only randomized clinical trials (RCTs) showing good methodological quality and assessing the effect of adjuvant intravenous immunoglobulin in the treatment of neonatal sepsis were selected for inclusion and data analysis.

Summary of the findings: Seven RCTs were selected. All of them evaluated the mortality rate, including 3,756 patients. The global effect of this outcome showed no statistically significant difference between the groups. Only five studies evaluated the mean length of hospital stay, including 3,672 patients. Although there is a statistically significant reduction of 1.24 days in the length of hospital stay with the use of intravenous immunoglobulin, such difference is clinically irrelevant and its high cost does not warrant its routine use in medical practice. The data reported in the present review contradict the review by Ohlsson et al., which was updated in 2010 and showed significant benefit with the use of intravenous immunoglobulin on both outcomes.

Conclusions: We concluded that the use of adjuvant intravenous immunoglobulin shows no benefit regarding mortality, whereas the reduction in the length of hospital stay is irrelevant.

J Pediatr (Rio J). 2012;88(5):377-83: Intravenous immunoglobulin, neonatal sepsis, septic shock, sepsis, infection, newborn infant.

Introduction

Neonatal infections show peculiar characteristics that are not observed in any other period of life.[1,2] Newborns, especially premature infants, have a fragile physical barrier and an immature immune function, what make them susceptible to invading bacteria (which normally would be only colonizing bacteria).[1,2] Sepsis is one of the most common conditions in the neonatal period.[3] It is a clinical syndrome characterized by a systemic inflammatory response in the presence – or as the result – of a suspected or confirmed infection.[4]

Infant mortality remains high in Brazil, with a rate of 17.6 in 2008, according to data provided by the IT Department of the Brazilian Unified Health System (DATASUS). Most of these deaths occur in the neonatal period, with a rate of 10.3

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in 2008. Sepsis is an important cause of mortality in this period. Despite the advances in the treatment and intensive care, the global incidence of neonatal sepsis remains high, from one to eight cases/1,000 live births, associated with a case-fatality ranging from 10 to 50%.[5]

Intravenous immunoglobulin (IVIg) has been considered as an adjuvant in the treatment of neonatal sepsis.[6-8] Knowing the characteristics of the fetal immune system development and the defense mechanism failures to protect infants against neonatal pathogens has provided theoretical support for the use of IVIg.[9,10] IVIg is used to provide specific antibodies of the IgG class to be connected to cell-surface receptors, promoting opsonization, antibody-dependent cytotoxic activity, and complement activation, while increasing neutrophil chemotaxis.[8]

Although it has been demonstrated that the use of IVIg is safe, its effectiveness remains questionable.[11]

Thus, the objective of the present systematic review is to investigate whether the adjuvant use of IVIg reduces mortality and length of hospital stay in the treatment of neonatal sepsis.

Methods

The MEDLINE database was searched using the pubmed.gov digital library. Each keyword of interest was sought using the Medical Subject Headings vocabulary. The keywords used were: *sepsis*; *shock*, *septic*; *infection*; *immunoglobulin*, *intravenous*; and *infant*, *newborn*, which were combined using the following search strategy: [(*sepsis* OR *shock*, *septic* OR *infection*) AND *immunoglobulins, intravenous*] AND *infant, newborn*. To refine the search, we used the Therapy/Narrow methodological filter.

The title and abstract of each article were analyzed, and the eligible articles were selected for full text reading. The inclusion criteria were: to be a randomized clinical trial; to compare the use of IVIg with the use of standard antibiotic therapy; to be written in Portuguese, English or Spanish; and to be conducted in patients aged less than 28 days. The exclusion criteria were: follow-up losses higher than 20%; use of IVIg in the prophylaxis of patients with increased risk for sepsis; and inclusion of patients older than 28 days.

The full text of the selected studies was read and critically analyzed. Only those studies with a score higher than or equal to 3 on the instrument designed by Jadad et al.[12] were included in the final selection and data analysis.

We analyzed the following outcomes: mortality and length of hospital stay. Dichotomous variables were analyzed based on the difference in the absolute risk (AR), with its 95% confidence interval (95%CI) and the number needed to treat (NNT) or number needed to harm (NNH) using the CATmaker software. Continuous variables were analyzed using the difference between the means, with its 95%CI. We used the Review Manager 5.1.1 software to perform the meta-analysis.

Results

The review of the literature was completed in February 2012. We found 53 studies, of which nine[13-21] were selected for full text reading. Two other studies were selected for full text reading by means of manual search.[22,23]

Of the 11 selected studies, four articles were not included in the data analysis: the full text of one of the studies[18] was not available at the Regional Library of Medicine (BIREME) and three articles were excluded.[19-21] The reasons for exclusion were: low methodological quality (Jadad et al. < 3)[19,20] and the fact that one of the studies included patients aged up to 5 years[21] (Figure 1).

The main characteristics of the seven studies included are described in Tables 1 and 2.

Mortality

All studies provided data on mortality; 3,756 patients were analyzed regarding this outcome.

Only the study by Haque et al.[23] demonstrated a statistically significant result – showing benefits with the use of IVIg –, with reduced AR of 0.17 (95%CI 0.01-0.03) and NNT = 6.

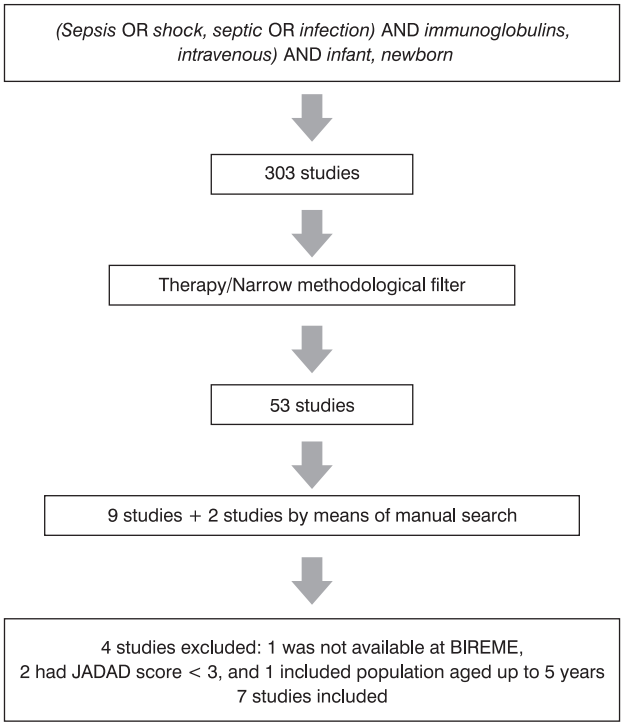


Figure 1 - Flowchart of the study selection

Table 1 - Characteristics of the studies included

Study	Population	Sample	Jadad
Brocklehurst et al.[13]	Confirmed or clinical sepsis with weight < 1,500 g or positive culture or need for ventilatory support	3,493	5
Ahmed et al.[22]	Clinical sepsis, GA < 33 weeks	60	3
Shenoi et al.[14]	Early clinical sepsis	58	3
Mancilla-R et al.[16]	Confirmed sepsis	37	4
Weisman et al.[15]	Early confirmed sepsis, weight between 500 and 2,000 g, GA < 34 weeks	31	3
Christensen et al.[17]	Early clinical sepsis	24	3
Haque et al.[23]	Clinical sepsis, GA 28-37 weeks	60	4

GA = gestational age.

The heterogeneity test (I^2) demonstrated homogeneity among the studies, except for the study by Haque et al.,[23] because this was the only study showing a statistically significant beneficial effect of IVIg (Figure 2). The heterogeneity is reduced from 35 to 0% when this study is excluded from the meta-analysis.

The combination of the effects from all studies, except for the one by Haque et al.,[23] reveals that there are no statistically significant differences (Figure 3). The difference between the AR of intervention and the AR of comparison is 0.00 (95%CI -0.03-0.02), NNT = 1,000.

Mean length of hospital stay

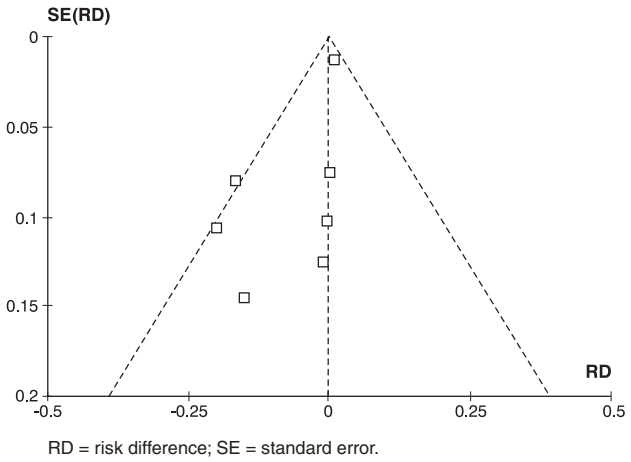
Only five studies[13-16,22] provided information on the mean length of hospital stay. Regarding this outcome, we analyzed 3,672 patients.

Only two studies showed statistically significant difference between the means of length of hospital stay of two groups. In the study by Mancilla-R et al.,[16] the IVIg group had 10.50 (95%CI 5.10-15.90) fewer days of hospital stay on average; and in the study by Ahmed et al.,[22] the IVIg group showed 3.77 (95%CI 0.94-6.60) fewer days of hospital stay on average.

Table 2 - Characteristics of the therapy regimens

Study	Intervention	Comparison	Associated treatment
Brocklehurst et al.[13]	IVIg Two doses of 500 mg/kg	Two doses of albumin 0.2%	Not reported
Ahmed et al.[22]	IVIg 500 mg/kg for 3 consecutive days	–	Not reported
Shenoi et al.[14]	IVIg 1 g/kg for 3 consecutive days	Saline solution 0.15% Dextrose 10% for 3 consecutive days	Not reported
Mancilla-R et al.[16]	IVIg One dose of 500 mg	10% maltose solution One dose	Ampicillin + amikacin
Weisman et al.[15]	IVIg One dose of 500 mg/kg	Albumin with 5% sucrose One dose of 5 mg/kg	Not reported
Christensen et al.[17]	5% IVIg in 10% maltose solution One dose of 750 mg/kg	Albumin 0.1 % + 10% maltose One dose of 15 mL/kg	Gentamicin + ampicillin Red blood cell transfusion in the first 3 days of life Albumin, is necessary
Haque et al.[23]	IgM-enriched IVIg 5 mL/kg/day for 4 days	Dextrose 10% 5 mL/day	Ampicillin (100 mg/kg/24 h) + gentamicin (3 mg/kg/24 h in NBs > 1 kg or 5 mg/kg/24 h in NBs < 1 kg)

IVIg = intravenous immunoglobulin; NBs = newborns.



RD = risk difference; SE = standard error.

Figure 2 - Funnel Plot: analysis demonstrating heterogeneity between the study by Haque et al.[23] and the other studies (the heterogeneous study is outside the funnel area)

The I^2 demonstrated homogeneity among the studies, except for the study by Mancilla-R et al.,[16] because this was the only study showing a higher beneficial effect of IVIg compared to the other studies (Figure 4). The heterogeneity is reduced from 75 to 38% when this study is excluded from the meta-analysis.

Although the other three studies[13-15] did not show any statistically significant differences in the mean length of hospital stay, the overall effect demonstrates a significant reduction of 1.24 days (95%CI 0.17-2.30) in the IVIg group (Figure 5).

Discussion

The present review of the literature showed no significant differences in the primary outcome (mortality) and demonstrated a significant reduction of 1.24 days in the mean length of hospital stay in the IVIg group. Regarding the primary outcome, only the study by Haque et al.[23] was heterogeneous in relation to the others, and in the secondary outcome, only the study by Mancilla-R et al.[16] was heterogeneous compared with the others.

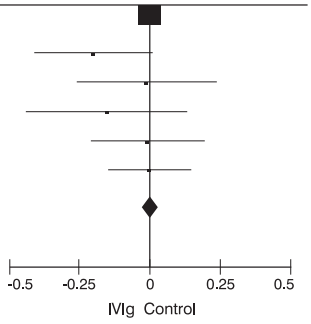
The I^2 shows and quantifies how heterogeneous the effects found in the studies are. The studies placed inside the funnel plot are homogeneous, whereas the studies outside the funnel plot are heterogeneous; therefore they cannot be compared and were excluded from the overall analysis. When there is high heterogeneity between the effects of the studies, the next step is to perform a sensitivity analysis, what can be done using diverse methods. Based on this scenario, we chose to revise the meta-analysis, excluding the heterogeneous studies.

The present review of the literature included seven articles.[13-17,22,23] The most recent article, Brocklehurst et al.,[13] is a multicenter study involving nine countries. Of the studies included, this was the most important one. It included a population of 3,493 patients, a sample much larger than that of the other studies, whose samples ranged from 24 to 60 patients. This was the only study with a score of 5 according to the instrument designed by Jadad et al.[12]

The study by Ahmed et al.[22] was conducted in Bangladesh and it was not found in the search of the main articles, being retrieved by means of manual search. The authors knew this study because it was included in the last systematic review[11] published on the same topic. This study did not describe the therapy used in the control group and it had

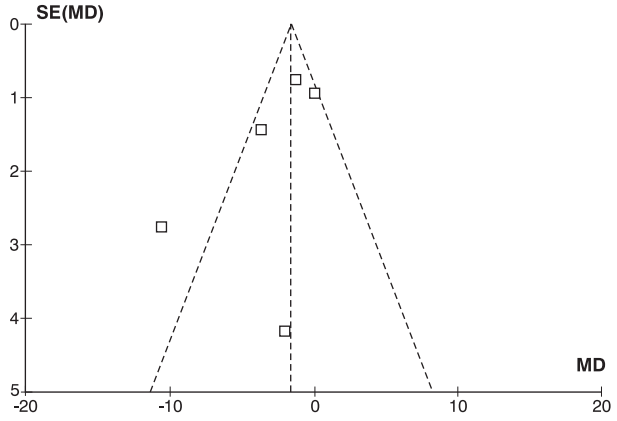
Study or Subgroup	IVIg Events	IVIg Total	Control Events	Control Total	Weight	Risk difference M-H, Fixed, 95%CI
Brocklehurst et al.[13]	322	1,759	306	1,734	94.5%	0.01 [-0.02, 0.03]
Ahmed et al.[22]	4	30	10	30	1.6%	-0.20 [-0.41, 0.01]
Shenoi et al.[14]	7	26	7	25	1.4%	-0.01 [-0.26, 0.23]
Weisman et al.[15]	2	14	5	17	0.8%	-0.15 [-0.44, 0.13]
Mancilla-R. et al.[16]	2	19	2	18	1.0%	-0.01 [-0.21, 0.19]
Christensen et al.[17]	0	12	0	12	0.6%	0.00 [-0.15, 0.15]
Total (95%CI)		**1,860**		**1,836**	**100%**	**0.00 [-0.02, 0.03]**
Total events	337		330			

Heterogeneity: $Chi^2 = 4.89$, df = 5 (P = 0.43); $I^2 = 0\%$
Test for overall effect: Z = 0.12 (P = 0.90)



95%CI = 95% confidence interval; IVIg = intravenous immunoglobulin; M-H = Mantel-Haenszel.

Figure 3 - Meta-analysis of the selected studies. Overall result expressed as difference of absolute risk, demonstrating a difference of 0.00 (95% confidence interval -0.03-0.02) and number needed to treat = 1,000



MD = mean difference; SE = standard error.

Figure 4 - Funnel Plot: analysis demonstrating heterogeneity between the study by Mancilla-R et al.[16] and the other studies (the heterogeneous study is outside the funnel area)

a score of 3 according to Jadad et al.[12] because it did not include a blinding procedure.

The study by Shenoi et al.[14] was conducted at three tertiary neonatal intensive care units in the city of Bangalore, India. It included patients with suspected sepsis based on clinical signs and it had a score of 3 according to the scale suggested by Jadad et al.[12] There were no significant differences in terms of mortality and length of hospital stay among the centers. This clinical trial was concluded early because of the withdrawal of financial support from the pharmaceutical company (Sandoz, India) that provided the drug used in the study at a lower cost.

The study by Mancilla-R et al.[16] was conducted in Mexico. It was a randomized trial, but the authors did not describe the method used for randomization. It had a score of 4 on the scale by Jadad et al.[12] This was the only heterogeneous study in comparison with the others regarding to the outcome mean length of hospital stay and, therefore, it was excluded from our overall analysis.

The study by Weizman et al.[15] was a multicenter study involving two research arms: the use of IVIg to prevent neonatal sepsis and the use of IVIg in the treatment of neonatal sepsis. The results on prevention were ignored in the present review. Its sample included only 31 patients, and albumin solution placed in bottles identical to the ones used for the study drug was used as placebo.

Christensen et al.[17] conducted a multicenter study without blinding, and its score according to Jadad et al.[12] was 3. This is the study with the smallest sample (24 patients).

The study by Haque et al.[23] was conducted in Saudi Arabia. It was not found in the search of the main articles as well, being retrieved by means of manual search. It had a score of 4 according to Jadad et al.[12] because the authors did not describe the randomization method. This study was heterogeneous in relation to the others in terms of the outcome mortality; thus, it was excluded from our overall analysis.

Of the studies included in our review, only those by Brocklehurst et al.,[13] Shenoi et al.,[14] and Weisman et al.[15] calculated the size of the sample in study design.

In relation to the population of these studies, the studies by Mancilla-R et al.[16] and Weizman et al.[15] included only patients with sepsis confirmed by culture; three studies[14,15,17] included only early sepsis; and the studies by Weizman et al.[15] and Ahmed et al.[22] included only premature infants (Table 1).

The therapy regimens of IVIg were different among the studies, as well as the regimen applied to the control groups. Only the studies by Mancilla-R et al.,[16] Christensen et al.,[17] and Haque et al.[23] mentioned the adjuvant therapy regimens (Table 2).

The review of the literature published by Ohlsson et al.,[10] which was updated in 2010, also evaluated the therapeutic use of IVIg in neonatal sepsis in 10 studies.[14-19,22-25] The study of Brocklehurst et al.,[13] which

	IVIg			Control				Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95%CI	IV, Fixed, 95%CI
Brocklehurst et al.[13]	64	28	1,759	64	28	1,734	32.2%	0.00 [-1.86, 1.86]	
Ahmed et al.[22]	14.53	3.88	30	18.3	6.88	30	14.3%	-3.77 [-6.60, -0.94]	
Shenoi et al.[14]	17	2.08	26	18.3	3.24	25	50.8%	-1.30 [-2.80, 0.20]	
Weisman et al.[15]	60.06	9.1	14	62.1	13.9	17	1.7%	-2.04 [-10.19, 6.11]	
Total (95%CI)		**1,829**			**1,806**		**100%**	**-1.24 [-2.30, -0.17]**	

Heterogeneity: Chi^2 = 4.83, df = 3 (P = 0.18); I^2 = 38%
Test for overall effect: Z = 2.26 (P = 0.02)

95%CI = 95% confidence interval; IVIg = intravenous immunoglobulin; IV = inverse variance; SD = standard deviation.

Figure 5 - Meta-analysis of the selected studies. Overall result expressed as mean difference, demonstrating a mean length of hospital stay of 1.24 (95% confidence interval 0.17-2.30) fewer days in the intravenous immunoglobulin group

had the largest sample and the best methodological quality, was not assessed in the review by Ohlsson et al.[11] because it was published later. Four other studies were included in the review by Ohlsson et al.[11] but were not evaluated in our review, namely: the study by Chen et al.,[19] because it had a score < 3 according to Jadad et al.[12]; the study by Erdem et al.,[18] because the text was not available at BIREME; the study by Samatha et al.,[24] because it was not found in any indexed basis; and the study by Sidiropoulos et al.,[25] because it was written in German.

The review by Ohlsson et al.[11] provided some information on these three studies,[18,24,25] which were not included in our review and whose full texts were not evaluated here, demonstrating that they were not consistent studies and did not have good methodological quality: the studies by Erdem et al.[18] and Sidiropoulos et al.,[25] for example, were not randomized trials; the study by Samatha et al.[24] was not a double-blind experiment; these three studies[18,24,25] did not use placebo and they have small samples of no more than 84 patients.

The inclusion of these three studies (Erdem et al.,[18] Samatha et al.,[24] and Sidiropoulos et al.[25]), as well as the studies excluded by Jadad < 3[19-21] would decrease the methodological quality of the present review, since we tried to evaluate only studies with good methodological quality; thus, such studies probably would not change the overall result because they had low relevance. In addition, the present review included the study by Brocklehurst et al.,[13] which was published in September 2011, with a much larger sample and better methodological quality compared to the other studies that were previously published and analyzed. This highlights the quality and validity of our review.

The data analysis of the review by Ohlsson et al.[11] showed statistically significant reduction in the relative risk of mortality as a consequence of the use of IVIg in 58% (95%CI 38-89%) and 55% (95%CI 31-98%) in the studies that included patients with clinical sepsis and confirmed sepsis, respectively.

In relation to the length of hospital stay, the review by Ohlsson et al.[11] also showed a statistically significant difference between the groups. IVIg reduced the length of hospital stay by 3.77 days (95%CI 0.94-6.60) in the studies that included preterm newborns with confirmed sepsis and by 2.99 days (95%CI 0.32-5.67) in the studies that included mainly term newborns with clinical sepsis.

Until this review was published, this was the best evidence available in the literature. However, the authors concluded that although the results are statistically significant, the low methodological quality of the studies could adversely affect its validity. Therefore, further studies with larger samples and good methodological quality are needed to support the routine use of IVIg.

The analysis of our findings reveals that the inclusion of the study by Brocklehurst et al.[13] changes the overall result of the meta-analysis compared with the results found in the review by Ohlsson et al.,[11] because this study is the most relevant and its results did not show significant differences.

Our review demonstrated that the primary outcome (reduced mortality rate) showed no differences between the intervention and control groups. Furthermore, it demonstrated that although there is a statistically significant reduction in the length of hospital stay in the IVIg group, such difference is clinically irrelevant and its high cost does not warrant its routine use in medical practice.

Conclusion

The present systematic review shows that there is no significant difference in the mortality rate with the adjuvant use of IVIg in the treatment of neonatal sepsis. Despite the statistically lower result in the IVIg group, the length of hospital stay showed clinically insignificant benefits.

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