Intravenous polyclonal IgM-enriched immunoglobulin therapy in sepsis: a review of clinical efficacy in relation to microbiological aetiology and severity of sepsis

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CRD summary
The authors concluded that patients with Gram-negative septic shock are most likely to benefit from immunoglobulin M-enriched intravenous polyclonal immunoglobulin (IVIG). However, given the unclear quality of included studies and the potential for reviewer error and bias, the authors’ conclusions should be treated with caution.

Authors’ objectives
To assess the efficacy of IgM-enriched intravenous polyclonal immunoglobulin (IVIG) in the treatment of patients with sepsis.

Searching
MEDLINE database and relevant published Cochrane reviews were searched. Search terms and dates were not reported.

Study selection
Controlled studies of IgM-enriched IVIG treatment in patients with sepsis were eligible for inclusion. Included studies were of IgM-enriched IVIG; dosages ranging from 200mg/100g to 500mg/100g. Control conditions in the included studies were no intervention, 10% dextran or 5% albumin. Study designs included for review were prospective randomised controlled trials (RCTs), prospective matched controls and retrospective case-control. Outcomes reported in included studies were mortality rates and Acute Physiology and Chronic Health Evaluation II (APACHE) score. Studies were excluded from the review where there were historical controls, where controls received fresh frozen plasma or where sepsis patients were only identifiable through subgroup analysis. Included studies were of neonates and paediatric patients or adolescent and adult populations. Three studies were exclusively of patients with severe sepsis or septic shock. One study was exclusively of patients with Gram-negative sepsis. Inclusion criteria for outcomes were not defined.

The authors did not state how the studies were selected for review or how many reviewers performed the study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The numbers of deaths in treatment and control groups were extracted to enable calculation of odds ratios (ORs) with 95% confidence intervals (CI) for each study. Authors were contacted for further information. The authors did not state how the data were extracted for the review or how many reviewers performed the data extraction.

Methods of synthesis
Pooled odds ratios (ORs) with corresponding 95% confidence intervals (CI) were combined in a meta-analysis using a fixed-effect model. Heterogeneity was calculated using the $\chi^2$ statistic. A subgroup analysis was conducted excluding non-randomised studies. Differences between the studies, in terms of outcomes for patients with Gram-negative sepsis and patients with severe sepsis, were explored by carrying out subgroup analyses for individual studies (where this data was available) and combining the results in a narrative synthesis.

Results of the review
Ten studies were included for review (n=645): eight prospective RCTs (n=492), one prospective matched controls (n=87) and one retrospective case-control study (n=66).

Overall Mortality:
Treatment with IgM-enriched IVIG was associated with a significant reduction in mortality (OR= 0.35, 95% CI: 0.23, 0.54, p<0.00001) compared to placebo or no intervention. There was no evidence of statistical heterogeneity. The authors reported that when non-randomised studies were excluded from the model, no significant change in effect size was found.

One RCT including only patients with Gram-negative sepsis showed significant reduction in mortality compared to controls with no intervention (4% versus 32%, p=0.012). Subgroup analysis of patients with Gram-negative sepsis was possible in two studies. Both found a greater reduction in mortality rates in the treatment groups compared to controls (5.9% versus 15.8% in controls receiving 10% dextran and 11.8% versus 50% in no intervention controls, p<0.02).

Severe Sepsis or Septic Shock:

Two RCTs focusing exclusively on patients with severe sepsis or septic shock found a significant reduction in mortality in the treatment group compared to the control groups (p=0.012 and p<0.01). Subgroup analysis of patients with severe sepsis was carried out for two further studies. One retrospective case-control study found a significant benefit of treatment in patients with severe sepsis when compared to controls (p=0.04), whereas one RCT found no significant benefit with treatment for patients with severe sepsis.

Authors' conclusions
Gram-negative septic shock patients are most likely to benefit from IgM-enriched IVIG.

CRD commentary
The review addressed a clear question and inclusion criteria were well defined for intervention and participants. Inclusion criteria for study design were unclear and outcomes were not pre-defined. Only one database was searched and no attempts appear to have been made to identify unpublished studies; therefore, relevant data may have been omitted and publication bias may have been introduced. Furthermore, it is unclear whether restrictions around language were applied, consequently language bias cannot be ruled out. There was insufficient information about the review process to rule out the possibility of reviewer error and bias in study selection or data extraction. A validity assessment was not carried out and there was insufficient information about the characteristics of included studies for the reader to make an assessment of study quality for themselves. The method of synthesis appeared appropriate. However, given the unclear quality of included studies and the potential for reviewer error and bias, the authors' conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further large scale trials are needed targeting specific patient cohorts.

Funding
Swedish Research Council; Swedish Foundation for Strategic Research.

Bibliographic details

PubMedID
17116001

DOI
10.1111/j.1365-2796.2006.01726.x

Indexing Status
Subject indexing assigned by NLM

MeSH
Adjuvants, Immunologic /therapeutic use; Gram-Negative Bacteria /immunology; Humans; Immunoglobulin G /immunology /therapeutic use; Immunoglobulin M /immunology /therapeutic use; Immunoglobulins, Intravenous /immunology /therapeutic use; Immunologic Factors /immunology /therapeutic use; Sepsis /immunology /microbiology /therapy; Severity of Illness Index; Treatment Outcome

AccessionNumber
12006009255

Date bibliographic record published
07/11/2007

Date abstract record published
29/04/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.