Intravenous immunoglobulin for sepsis (severe sepsis and septic shock)

An evaluation of the feasibility, cost and value of information of a multicentre randomised controlled trial of intravenous immunoglobulin for sepsis (severe sepsis and septic shock): incorporating a systematic review, meta-analysis and value of information analysis

MO Soares,[1] NJ Welton,[2] DA Harrison,[3] P Peura,[1] M Shankar-Hari,[4] SE Harvey,[3] JJ Madan,[2] AE Ades,[2] SJ Palmer[1] and KM Rowan[3]*

[1]Centre for Health Economics, University of York, York, UK
[2]School of Social and Community Medicine, University of Bristol, Bristol, UK
[3]Intensive Care National Audit & Research Centre, London, UK
[4]Guy's and St Thomas' Hospital NHS Foundation Trust, London, UK

*Corresponding author

Executive summary

Health Technology Assessment 2012; Vol. 16: No. 7
DOI: 10.3310/hta16070

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

Executive summary

Background

Sepsis is a syndrome characterised by a systemic inflammatory response to infection that leads to rapid acute organ failure and potentially rapid decline to death. Estimates of severe sepsis (sepsis associated with acute organ dysfunction) in UK adult critical-care units from the Intensive Care National Audit & Research Centre Case Mix Programme Database indicate an increasing incidence of severe sepsis in critical care (rising from 50 to 70 cases per 100,000 population per year over the last decade). This now represents approximately 31,000 patient episodes and 15,000 in-hospital deaths per year.

Intravenous immunoglobulin (IVIG), a blood product derived from human donor blood, has been proposed as an adjuvant therapy for sepsis. Numerous systematic reviews and meta-analyses of IVIG in sepsis have been performed. As a result of heterogeneity across studies and inconsistencies in results, the majority have concluded that more evidence, in the form of a large, well-conducted randomised controlled trial (RCT), is required.

Intravenous immunoglobulin is a scarce resource worldwide. Costs have escalated, associated with a reduced demand for plasma-derived factor VIII and albumin, and there are supply issues, unique to the UK, that further limit its availability. The Department of Health Demand Management Programme for IVIG indicates that treatment is not recommended for severe sepsis. The associated clinical guidelines recommend the need for an adequately powered, high-quality RCT.

There is an urgent need to establish whether or not such a trial is necessary and feasible and whether or not the costs of carrying out the trial are outweighed by the potential benefit of the resulting information.

Objectives

- To describe current practice in the management of adult patients severely ill with sepsis (severe sepsis or septic shock) in the UK.
- To assess the clinical effectiveness of IVIG for severe sepsis and septic shock, and to obtain the appropriate inputs for the relative efficacy parameters and the key uncertainties associated with these parameters, required to populate the decision model.
- To develop a decision-analytic model structure and identify key parameter inputs consistent with the decision problem and relevant to an NHS setting.
- To populate the decision model and determine the cost-effectiveness of IVIG and to estimate the value of additional primary research.

Methods

Survey

A national survey of clinical directors of adult, general critical-care units in the UK was conducted. Items selected for inclusion in the survey were those that were ranked as Level 1A or Level 1B in the Surviving Sepsis Campaign (SSC) guidelines and components of the resuscitation and management bundles for sepsis developed by the SSC.

Clinical effectiveness

A systematic review of the literature was carried out. Stage 1 reviewed previous systematic reviews. Stage 2 updated the most relevant of these previous systematic reviews (a Cochrane review) using the following databases: the Cochrane Infectious Diseases Group Specialized Trials Register, the Cochrane Trials Register, MEDLINE and EMBASE. Dates searched were 1 January 2002 to 2 October 2009 to update previous Cochrane review. Stage 3 examined the list of excluded studies from the existing Cochrane review and Stage 4 reviewed an update to the existing Cochrane review. All studies were assessed for inclusion in our review against our criteria.

Randomised controlled trials within a critical-care setting that compared any standard polyclonal IVIG or immunoglobulin M-enriched polyclonal IVIG (IVIGAM) with no intervention, placebo, or another standard polyclonal IVIG or IVIGAM preparation were considered eligible for inclusion. Studies were included if the majority of patients were aged ≥ 18 years and clinical judgement deemed the population studied to have severe sepsis or septic shock. The primary outcome measure extracted was all-cause mortality. Information was also extracted, where available, on study: details, quality, population, intervention and any reported adverse events.

All-cause mortality was summarised on the odds ratio (OR) scale. Forest plots were produced to display results across studies for both fixed- and random-effects models using inverse variance weights. Heterogeneity was assessed using the I^2 measure and Cochrane Q-statistic. Publication bias was investigated by inspecting a funnel plot for asymmetry. A more formal modelling selection process, using Bayesian Markov chain Monte Carlo simulation, was performed to identify the key covariates responsible for heterogeneity, to consider more complex treatment models that compared different types and preparations of IVIG and for considering combinations of covariates to adjust for potential confounding.

Cost-effectiveness and value of information analysis

A decision model was developed to evaluate the use of IVIG (as an adjunct to standard care) compared with standard care in adults with severe sepsis. A systematic review of the cost-effectiveness literature was conducted. Databases searched were NHS EED to 2 October 2099, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE to 20 October 2009. Further searches were conducted to inform relevant model parameters. The decision model was used to estimate the cost-effectiveness of IVIG in terms of cost per quality-adjusted life-year (QALY) under a range of assumptions. Decision uncertainty associated with this analysis was presented and used to inform future research priorities using the value of information analysis.

The impact of uncertainties related to input parameters and assumptions was assessed. Alternative data aggregation models over the effectiveness of IVIG were fully evaluated for their impact over cost-effectiveness (and decision uncertainty) and for their impact on the need for further research. Consistent with available evidence, the model also explored variability in the cost-effectiveness estimates for specific subgroups of patients.

Results

Survey

Of 231 adult, general critical-care units, a dedicated senior clinician could not be identified for 14. Of the remaining 217 units, respondents at four (2%) units refused to complete the survey and completed surveys were received for 123 (57%) units.

The survey indicated that there has been high uptake (> 70%) of bundles for the resuscitation and management of patients with severe sepsis, predominantly those recommended by the SSC.

The responses to the survey indicated that, despite variation across units, usual clinical practice for patients with severe sepsis can be broadly summarised into immediate resuscitation and advanced management, as follows.

Resuscitation

- Take blood cultures.
- Give intravenous antibiotics within 1 hour.
- Maintain serum lactate < 4 mmol/l.
- Fluid resuscitate using a combination of crystalloids and colloids.
- Maintain mean arterial pressure ≥ 65 mmHg.
- Maintain central venous pressure ≥ 8 mmHg (or 10–15 mmHg for mechanically ventilated patients).
- Give noradrenaline for hypotension not responding to initial fluid resuscitation.
- Maintain central venous oxygen saturation or mixed venous oxygen saturation (SvO_2) ≥ 70%.

Management

- Administer low-dose steroids in accordance with standardised critical care protocol.
- Administer recombinant human activated protein C in accordance with standardised critical care protocol.
- Maintain blood glucose levels within the range 4–10 mmol/l.
- Maintain inspiratory plateau pressure < 30 cmH_2O for mechanically ventilated patients.
- Give prophylaxis for deep-vein thrombosis.
- Give stress ulcer prophylaxis.

Seventy (56.9%) respondents reported that they use IVIG for the advanced management of patients. The clinical reasons given for administering IVIG included neurological diseases, toxin-mediated illnesses and other indications.

These results suggest that a protocolised/bundle approach to immediate resuscitation and advanced management, would need to be considered for the usual-care arm in any future multicentre RCT of IVIG as an adjunctive therapy in the advanced management of patients acutely ill with severe sepsis.

Clinical effectiveness

Seventeen studies met the inclusion criteria with a large degree of heterogeneity in treatment effect between studies. Modelling indicated that there were issues with bias associated with trial methodology, publication and small-study effects with the current evidence. The large degree of heterogeneity in treatment effects between studies, however, could be explained (best-fitting model) by a measure of study quality (i.e. use of albumin as control – as an indicator of proper blinding to treatment as a proxy for study quality – associated with decreased effect) and duration of IVIG therapy (longer duration associated with increased effect). In-depth discussion within the Expert Group on duration of IVIG therapy, with daily dose and total dose also clearly inter-related, indicated no clear clinical rationale for this association and exposed a lack of evidence on the understanding of the mechanism of action of IVIG in severe sepsis.

For a duration of 3 days (the most commonly used duration of therapy reported in the studies), there was an OR of 0.75 with 95% credible interval (0.58 to 0.96) showing a reduction in the odds of all-cause mortality in patients with severe sepsis using IVIG compared with albumin. When the heterogeneity explained by dosing regime was treated as unexplained heterogeneity (i.e. a random-effect models), the results still showed a reduction in the odds of all-cause mortality in patients with severe sepsis using IVIG compared with albumin (OR 0.68), but the credible intervals were widened (0.16 to 1.83) so that the result was no longer statistically significant.

Cost-effectiveness and value of information analysis

Only one published cost-effectiveness analysis of IVIG was identified, evaluating the short-term cost-effectiveness of a specific IgM-enriched product (not available in the UK) compared with standard care for severe sepsis/septic shock. Careful assessment of this study revealed that its findings were unlikely to be generalisable to UK clinical practice.

Literature searches identified 15 cost-effectiveness studies of other interventions for the management of severe sepsis using a range of different model structures and assumptions to model the costs and benefits. The variation in model design may be attributed to the sparse data available in the literature for most quantities of interest, especially long-term outcomes (e.g. mortality, quality of life) of survivors of severe sepsis. Primary data, collected in the UK, were used to strengthen our inferences.

The results of the cost-effectiveness analysis, using the best-fitting clinical effectiveness model (using duration of treatment) for all-cause mortality, gave an incremental cost-effectiveness ratio (ICER) of IVIG of £20,850 per QALY (incremental costs = £9308/incremental QALYs = 0.45), which is within the borderline region of estimates considered to be cost-effective in the NHS. At a threshold of £20,000 per QALY, the probability that IVIG is more cost-effective than standard care alone is 0.505.

When considering alternative models from the clinical effectiveness review, the ICER estimates vary between £16,177 per QALY to IVIG being dominated by standard care alone (i.e. IVIG being both less effective and more costly). These results clearly demonstrate that any conclusions regarding the cost-effectiveness of IVIG are highly sensitive to the choice of model used for clinical effectiveness.

Given the uncertainty surrounding the long-term survival extrapolation required to estimate lifetime QALY gains, the robustness of the results to alternative assumptions was explored. By varying the time horizon, the cost-effectiveness of IVIG was shown to be dependent upon the additional QALY gains predicted as part of the longer-term extrapolation. However, the time point at which sepsis survivors were assumed to revert back to general population mortality rates did not appear to be a key driver of cost-effectiveness.

Owing to the absence of UK data on the costs associated with longer-term management of sepsis survivors, this issue was further explored. The assumption that patients continue to incur higher costs than the general population over the longer-term extrapolation period was revealed to be an important consideration.

Population estimates of the expected value of perfect information varied substantially, depending on the clinical effectiveness model applied to estimate the relative effectiveness of IVIG. However, in the majority of scenarios, a study collecting data on the relative effectiveness of IVIG (in relation to standard care) was shown to be the most efficient research design to invest in. Furthermore, it is not clear whether or not there is any clinical rationale for the effects explored within each of the clinical effectiveness models and so, although the need for a further RCT exists, designing this study is complex when uncertainties at this level exist.

Conditional on accepting the best-fitting model (using duration of treatment) as valid, the optimal sample size for a RCT was determined by evaluating the expected net benefit of sampling. For a range of per-patient costs associated with conducting this trial (from £2000 to £35,000) the optimal sample size varied from 500 to 1900 subjects in each arm (assuming equal allocation between arms).

Research informing the long-term survival and costs of severe sepsis survivors may also be of value, although this result was not consistent across the scenarios explored. Whether or not conducting this research is relevant is thus still dependent on clarifying the results on clinical effectiveness by further understanding the mechanism of action of IVIG and the heterogeneous nature of severe sepsis.

Conclusions

Implications for health care

Our meta-analysis, the first to simultaneously allow for type of IVIG (IVIG or IVIGAM), choice of control (no treatment or albumin), study quality/publication bias and other potential covariates, indicated that the treatment effect of IVIG on mortality for patients with severe sepsis is borderline significant with a large degree of heterogeneity in treatment effect between individual studies. Based on the results of combining the available evidence, and until further evidence becomes available, the immediate implications for health care are as per current policy and practice for off-label use of IVIG in severe sepsis (i.e. colour coded black, as treatment not recommended).

Recommendations for research

Although the expected value of information (EVI) analyses suggested substantial expected net benefit from a large multicentre RCT evaluating the clinical effectiveness of IVIG, the remaining uncertainties around the design of such a study mean that we are unable to recommend it at this time. Our recommendations for research focus on filling the knowledge gaps to inform a future multicentre RCT prior to recommending its immediate design and conduct.

Recommendation 1

Research on the mechanism(s) of action of IVIG preparation(s) in the severe sepsis population commencing with a thorough review of existing research prior to embarking on any new research.

Recommendation 2

Informed by *Recommendation 1*, dose-ranging/finding studies to identify dose, timing of dose and safety data (tolerability/side-effects) to inform the intervention(s) for a future multicentre RCT.

Recommendation 3

Research to inform the long-term survival, including quality and costs of survival, for the severe sepsis population.

Recommendation 4

Results of *Recommendation(s) 1–3* should be re-evaluated for their impact on our EVI analyses.

Recommendation 5

Recommendation(s) 1–3 require knowledge of, and design of the definitive RCT for IVIG in severe sepsis requires a comprehensive review of, the emerging evidence surrounding the heterogeneity of the severe sepsis population at the genetic, biochemical and clinical level.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Publication

Soares MO, Welton NJ, Harrison DA, Peura P, Shankar-Hari M, Harvey SE, *et al.* An evaluation of the feasibility, cost and value of information of a multicentre randomised controlled trial of intravenous immunoglobulin for sepsis (severe sepsis and septic shock): incorporating a systematic review, meta-analysis and value of information analysis. *Health Technol Assess* 2012;**16**(7).

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/70/01. The contractual start date was in May 2009. The draft report began editorial review in September 2010 and was accepted for publication in February 2011. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.