Protocolised Management In Sepsis (ProMISe): a multicentre randomised controlled trial of the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock

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Scientific summary

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Background

The incidence of severe sepsis and septic shock in adults is estimated to range from 56 to 91 per 100,000 population per year. Affected patients have high mortality, morbidity and resource utilisation.

Since 2002, the Surviving Sepsis Campaign has promoted best practice, which includes early recognition, source control, appropriate and timely antibiotic administration, and resuscitation with intravenous fluids and vasoactive drugs. Resuscitation guidance is largely based on a 2001 single-centre, proof-of-concept trial, which indicated that protocolised delivery of 6 hours of early goal-directed therapy (EGDT) to patients presenting at the emergency department (ED) with early septic shock reduced hospital mortality and hospital length of stay. EGDT aims to optimise tissue oxygen transport using continuous monitoring of pre-specified physiological targets – central venous pressure, mean arterial pressure and central venous oxygen saturation ($ScvO_2$) – to guide the delivery of intravenous fluids, vasoactive drugs and packed red blood cell transfusions.

However, despite Surviving Sepsis Campaign recommendations, adoption of EGDT has been limited, with concerns about the external validity of results from a single-centre trial, the complexity of protocol delivery, the potential risks of the components and the resources required for implementation.

To address these concerns, multicentre trials of EGDT in the USA (Protocolized Care for Early Septic Shock: ProCESS), Australasia (Australasian Resuscitation In Sepsis Evaluation: ARISE) and England (Protocolised Management In Sepsis: ProMISe) were conducted, employing harmonised methods to permit an individual patient data meta-analysis.

The ProMISe trial tested the hypothesis that the 6-hour EGDT resuscitation protocol is superior, in terms of clinical effectiveness and cost-effectiveness, to usual resuscitation in patients presenting with early septic shock to NHS EDs in England.

Objectives

The primary objectives of the trial were:

- to estimate the effect of EGDT compared with usual resuscitation on all-cause mortality at 90 days
- to compare incremental cost-effectiveness at 1 year of EGDT with usual resuscitation.

The secondary objectives were to compare EGDT with usual resuscitation for:

- requirement for, and duration of, critical care unit organ support
- length of stay in the ED, critical care unit and acute hospital
- health-related quality of life at 90 days and at 1 year
- resource use and costs at 90 days and at 1 year
- all-cause mortality at 28 days, at acute hospital discharge and at 1 year
- estimated lifetime incremental cost-effectiveness.

Methods

Trial design and governance

ProMISe was a pragmatic, open, multicentre, parallel-group randomised controlled trial. The North West London Research Ethics Committee approved the trial. The UK National Institute for Health Research funded the trial and convened a Trial Steering Committee and an independent Data Monitoring and Ethics Committee. The Clinical Trials Unit at the Intensive Care National Audit & Research Centre (ICNARC) managed the trial. The trial was prospectively registered for an International Standard Randomised Controlled Trial Number (ISRCTN36307479).

Participants: sites and patients

The trial was conducted in English NHS hospitals not routinely using EGDT including continuous $ScvO_2$ monitoring. Patients aged 18 years or over were eligible if, within 6 hours of ED presentation, they had a known or presumed infection, two or more systemic inflammatory response syndrome criteria, and either refractory hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg, despite intravenous fluid resuscitation of at least 1 l within 60 minutes) or hyperlactataemia (blood lactate concentration ≥ 4 mmol/l) and did not meet any exclusion criteria.

Randomisation had to be completed within 2 hours of meeting inclusion criteria following informed consent from the patient or agreement from a personal/professional consultee or an independent clinician. Patients were allocated in a 1 : 1 ratio, via 24-hour telephone randomisation, to EGDT or usual resuscitation. Allocation was by randomised permuted blocks, with variable block lengths, stratified by site. Antimicrobials had to be commenced prior to randomisation.

Treatment groups

Following randomisation, the usual-resuscitation group continued to receive monitoring, investigations and treatment determined by the treating clinician(s) while the EGDT group commenced the resuscitation protocol. For the latter, during the first hour, a central venous catheter capable of continuous $ScvO_2$ monitoring was inserted. The resuscitation protocol was followed for 6 hours (intervention period) with personnel involved and treatment location decided by sites, although at least one trained member of staff was available throughout. All other treatment, during the intervention period and after, was at the discretion of the treating clinician(s). Blinding to treatment allocation was not possible. Edwards Lifesciences Ltd (Newbury, Berkshire) lent monitors and provided training and technical support, but had no other role in the trial.

Data sources

A secure, dedicated electronic case report form was set up to enable trial data to be entered by staff at participating sites. Inclusion criteria, baseline, intervention, physiology and location of care data to the point of hospital discharge were collected by the sites. Following linkage with the Health and Social Care Information Centre Data Linkage and Extract Service to confirm mortality status, a Health Services Questionnaire and a European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire were sent to patients at 90 days and 1 year. These provided information about the patient's use of health services and quality of life following discharge from the acute hospital. Linkage to the ICNARC Case Mix Programme database provided information on subsequent admission to adult general critical care following discharge from the acute hospital.

Analysis principles

All analyses were by intention to treat, following a pre-specified statistical analysis plan. A p-value of 0.05 was considered statistically significant. All tests were two-sided with no adjustment for multiple comparisons. As missing data for the clinical effectiveness primary outcome were anticipated to be minimal, a sensitivity approach was taken when the primary outcome was missing. Missing data for the cost-effectiveness analysis, as well as missing baseline data for adjusted analysis of clinical outcomes, were handled by multiple imputation using chained equations.

Outcome measures

The primary clinical effectiveness outcome was all-cause mortality at 90 days. The primary cost-effectiveness outcome was incremental net monetary benefits (INBs) at £20,000 per quality-adjusted life-year (QALY) at 1 year. Secondary outcomes were Sequential Organ Failure Assessment (SOFA) score at 6 and 72 hours; receipt of and days alive and free (up to 28 days) from advanced cardiovascular, advanced respiratory or renal support; ED, critical care and acute hospital length of stay; duration of survival; all-cause mortality at 28 days, at acute hospital discharge and at 1 year, and health-related quality of life (measured by the EQ-5D-5L questionnaire), resource use, and costs at 90 days and 1 year, and lifetime incremental cost-effectiveness. Adverse events were monitored to 30 days. The cost-effectiveness analysis estimated INBs by valuing incremental QALYs at the threshold value for a QALY gain (£20,000) that is recommended by the National Institute for Health and Care Excellence and then subtracting the incremental costs.

Secondary analyses of the primary outcomes included adjusted analysis [adjusted for Mortality in Emergency Department Sepsis (MEDS) score components], learning curve analysis (clinical effectiveness only) and adherence-adjusted analysis. Pre-specified subgroup analyses were conducted, testing interactions between the effect of EGDT and the following: degree of protocolised care for usual resuscitation; age; MEDS score; SOFA score; and time from ED presentation to randomisation. Sensitivity analyses were performed for missing data in the primary clinical outcome and to test the main assumptions of the cost-effectiveness analysis.

Results

Sites and patients

In total, 6192 patients were screened at 56 sites, with 1260 enrolled between 16 February 2011 and 24 July 2014. Four patients requested complete withdrawal and five were ineligible, resulting in 1251 patients for initial analysis (625 EGDT and 626 usual resuscitation). Eight patients withdrew before 90 days, resulting in 1243 patients for analysis of outcomes (623 EGDT and 620 usual resuscitation). Groups were well matched at baseline.

Adherence to protocol

Most patients randomised to EGDT had timely insertion of a central venous catheter capable of continuous $ScvO_2$ monitoring; two, inserted in error in the usual-resuscitation group, were not used for monitoring $ScvO_2$. Standard central venous catheters (not mandated) were inserted in 50.9% of the usual-resuscitation group and $ScvO_2$ measurement from aspirated blood samples occurred in six patients. Arterial catheters (not mandated) were inserted in most patients. EGDT was stopped prematurely in 21 patients. Overall, adherence to EGDT was good.

Delivery of care by treatment group

During the 6-hour intervention period, EGDT patients received more intravenous fluid. Hourly fluid volume decreased over the 6 hours but usual-resuscitation patients received a larger initial volume. In both groups, crystalloid was used more frequently. More EGDT patients received vasopressors and dobutamine. Although more EGDT patients received packed red blood cells, larger volumes were transfused in the usual-resuscitation group. During the 6-hour intervention period, administration of platelets and fresh-frozen plasma was similar, although volumes of both were higher in the EGDT group. At 6 hours, central venous pressure, mean arterial pressure, systolic blood pressure and haemoglobin, where measured (greater frequency in the EGDT group), were similar.

Between 6 and 72 hours, use of intravenous fluids was similar but usual-resuscitation patients received higher volumes. Intravenous colloid use was higher in EGDT patients but volumes were similar in the two groups, intravenous crystalloid use was similar but volumes were higher in usual-resuscitation patients and use of packed red blood cells was higher in EGDT patients but the volumes delivered were higher in usual-resuscitation patients. Although use of platelets and fresh-frozen plasma was similar, the volume of

platelets transfused was higher in EGDT patients and the volume of fresh-frozen plasma was higher in usual-resuscitation patients. Vasopressor and dobutamine use remained higher in EGDT patients. At 72 hours, physiological, biochemistry and SOFA values were similar.

Primary outcome: clinical effectiveness

At 90 days following randomisation, 184 (29.5%) patients randomised to EGDT had died, compared with 181 (29.2%) patients randomised to usual resuscitation, corresponding to an absolute risk reduction of −0.3 [95% confidence interval (CI) −5.4 to 4.7; $p = 0.90$] and a relative risk of 1.01 (0.85 to 1.20). This difference remained non-significant after adjustment for baseline characteristics (adjusted odds ratio 0.95, 95% CI 0.74 to 1.24; $p = 0.73$; unadjusted odds ratio 1.02, 95% CI 0.80 to 1.30).

Secondary outcomes: clinical effectiveness

For EGDT patients, the mean SOFA score at 6 hours, the proportion receiving advanced cardiovascular support and the median critical care length of stay were significantly greater. No other secondary outcomes were significantly different. Thirty (4.8%) EGDT patients and 26 (4.2%) usual-resuscitation patients experienced one or more serious adverse events ($p = 0.58$).

Subgroup and secondary analyses

There was no difference in effect of EGDT according to pre-specified subgroups (*p*-values for test of interaction 0.39 to 0.72). Sensitivity analyses for missing primary outcomes (EGDT, $n = 2$; usual resuscitation, $n = 6$) reported relative risks from 0.99 to 1.03. There was no evidence of a learning-curve effect ($p = 0.56$). Adherence-adjusted analysis reported a relative risk of 1.02 (95% CI 0.78 to 1.32; $p = 0.90$).

Cost-effectiveness analysis

At 1 year following randomisation, a slightly higher proportion of EGDT patients than usual-resuscitation patients were alive. The net effect of EGDT patients having higher survival but a lower average patients European Quality of Life-5 Dimensions utility score resulted in similar 1-year QALYs between the treatment groups. The mean total cost was higher in EGDT patients, with an incremental cost of £764 (95% CI −£1402 to £2930), and hence the INB for EGDT versus usual resuscitation was negative at −£725 (95% CI −£3000 to £1550). The estimated INBs were similar for adherence-adjusted analysis and across all pre-specified subgroups. The estimated INBs were also similar for the alternative scenarios considered in the sensitivity analyses. The probability that EGDT is cost-effective, at the recommended threshold of £20,000 per QALY, is below 30%. Cost-effectiveness results were similar at 90 days (INB −£1000, 95% CI −£2720 to £720) and when extrapolated to the lifetime (INB −£1446, 95% CI −£8102 to £5210).

Conclusions

Among adults identified with early signs of septic shock presenting to the ED of one of 56 NHS hospitals in England and receiving 6 hours of protocolised resuscitation, there was no significant difference in mortality at 90 days, compared with usual resuscitation. Although mortality was lower than anticipated, these results rule out a relative risk reduction with EGDT of > 15%. On average, EGDT increased costs and, given similar QALYs across groups, INB at 1 year was negative. The probability that EGDT is cost-effective (at a willingness to pay of £20,000 per QALY) is below 30%.

There was no significant interaction between treatment effect and mortality at 90 days across pre-specified subgroups. More patients receiving EGDT were admitted to critical care, resulting in significantly more days spent in critical care in this group. Treatment intensity was greater for EGDT patients, driven by adherence to the protocol, and indicated by increased use of central venous catheters, intravenous fluids, vasoactive drugs and packed red blood cells. Increased treatment intensity was reflected in significantly higher SOFA scores and more advanced cardiovascular support days in critical care for the EGDT group. There were no significant differences in any other secondary outcomes including health-related quality of life, which was substantially poorer in this severely ill patient group at both 90 days and 1 year than for the age-/sex-matched general population.

Implications for health care

The results suggest that usual resuscitation has evolved over the 15 years since the Rivers *et al.* trial (Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;**345**:1368–77); NHS hospitals now achieve levels of in-hospital survival similar to those achieved with EGDT in the Rivers *et al.* trial for patients with septic shock identified early and receiving intravenous antibiotics and adequate fluid resuscitation. The addition of continuous $ScvO_2$ monitoring and strict protocolisation of care was, on average, more costly and did not improve outcomes.

Recommendations for research

Recommendation 1: an individual patient data meta-analysis of the three completed trials should be conducted

These results complete the planned trio of evaluations of EGDT across the USA, Australasia and England. Each has their own strengths and weaknesses, but all have indicated that EGDT is not superior to usual resuscitation. Recognising that each of the three individual large trials has limited power for evaluating potentially important subgroups, the harmonised approach adopted provides the opportunity to conduct an individual patient data meta-analysis, enhancing both knowledge and generalisability.

Recommendation 2: further research to consider alternative definitions of adherence to the resuscitation protocol should be conducted

Both the clinical effectiveness and cost-effectiveness analyses reported estimates that were adherence-adjusted as part of pre-specified secondary analyses. However, further research to consider alternative definitions of adherence to the EGDT resuscitation protocol are warranted. In particular, future research could apply differential weights for adherence to the different elements of the EGDT resuscitation protocol, or to particular time points within the 6-hour intervention period. Hence subsequent research could report whether EGDT was clinically effective or cost-effective when these alternative definitions of adherence were met.

Trial registration

This trial is registered as ISRCTN36307479.

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