CAGS AND ACS EVIDENCE BASED REVIEWS IN SURGERY. 31

The use of intensive insulin therapy and pentastarch resuscitation in patients with severe sepsis

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The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."[1] The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) and is supported by an educational grant from ETHICON and ETHICON ENDO-SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson and ETHICON Inc. and ETHICON ENDO-SURGERY Inc., divisions of Johnson & Johnson Inc. The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

Reference

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

Selected article

Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125-39.

Abstract

Question: Is the use of intensive insulin therapy compared with conventional therapy (on the basis of Leuven titration protocol) and hydroxyethyl starch (HES) compared with Ringer lactate effective and safe in patients with severe sepsis or septic shock? **Design:** Randomized open-label controlled trial. **Setting:** Multicentre (18 academic tertiary hospitals in Germany). **Patients:** Six hundred patients with a diagnosis of severe sepsis or septic shock. Patients were deemed to be eligible if the onset of the syndrome was less than 24 hours before admission to the intensive care unit (ICU) or less than 24 hours after admission if the condition developed in the ICU. **Interventions:** Patients were randomly assigned in a 2 × 2 factorial design to receive either conventional (target blood glucose 180–200 mg/dL; n = 326) or intensive insulin therapy (target blood glucose 80–100 mg/dL; n = 274) or HES (n = 207) or Ringer lactate (n = 303). **Main outcomes:** Death from any cause at 28 days and morbidity measured by the mean score on the Sequential Organ Failure Assessment (SOFA) on a scale ranging from 0 to 4 for each of 6 organ systems with an aggregate score of 0–24 and higher scores indicating more severe organ dysfunction. **Results:** The mean morning blood glucose level was lower in the intensive therapy group (112 mg/dL [6.2 mmol/L]) than in the conventional therapy group (151 mg/dL [8.4 mmol/L]; $p \leq 0.001$). However, at 28 days there were no significant differences between the groups in the rate of death or mean score for organ failure. The rate of severe hypoglycemia (glucose level ≤ 40 mg/dL [2.2 mmol/L]) was higher in the intensive therapy group than in the conventional therapy group (17% v. 4.1%; $p \leq 0.001$), as was the rate of serious adverse events (10.9% v. 5.2%, p = 0.010). Hydroxyethyl starch therapy was associated with higher rates of acute renal failure and renal replacement therapy than Ringer lactate. **Conclusion:** The use of the intensive insulin therapy placed critically ill patients with sepsis at an increased risk for serious adverse events related to hypoglycemia. As used in this study, HES was harmful and its toxicity increased with accumulating doses.

Commentary

Much about the optimal therapy of critically ill septic patients is controversial or unknown. In this multicentre randomized open-label controlled trial (the VISEP study), Brunkhorst and colleagues used a factorial design to evaluate 2 key components of resuscitation and early management: the selection of crystalloids versus colloids as a resuscitative solution and the risks and benefits of strict euglycemia through the use of insulin. Both questions have been hotly debated in critical care circles, and a brief background to each controversy is useful.

The optimal fluid for resuscitation has been the subject of a number of small clinical trials dating back to the 1970s. Proponents of colloids such as albumin or a variety of commercial starch solutions argue that these solutions are better able to maintain intravascular volume without producing edema and its adverse consequences. Proponents of crystalloids such as normal saline or Ringer lactate argue that altered vascular permeability in septic shock results in extravasation of colloids into the tissues, potentially worsening extravascular edema. In addition, they state that given the lack of obvious superiority for colloids, cost considerations render crystalloids the fluid of choice. A systematic review[1] of albumin therapy published in the late 1990s concluded that albumin use may result in excess mortality, although other similar reviews have not confirmed this. An Australian study[2] of 6997 patients in intensive care found comparable mortality rates associated with the use of albumin and crystalloid solution, but suggested that outcomes in patients with head injuries were worse with albumin use, whereas albumin use in septic patients led to improved outcomes.

Van den Berghe and colleagues[3] from Leuven, Belgium, reported in a single-centre trial that maintenance of strict euglycemia resulted in improved survival in a predominantly surgical population of critically ill patients. Subsequently in a group of medical patients, there was similar benefit, albeit only in those patients who remained in the ICU for 3 days or more. Other studies have failed to replicate this finding or have even found higher rates of hypoglycemia when euglycemia was targeted. Van den Berghe and colleagues' work has been influential, and many North American ICUs have implemented labour-intensive protocols for the maintenance of euglycemia.

Brunkhorst and colleagues examined intensive insulin therapy and pentastarch resuscitation in a multicentre randomized controlled trial of patients with severe sepsis. The Efficacy of volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study compared intensive insulin therapy with conventional insulin therapy and hydroxyethyl starch resuscitation with Ringer lactate resuscitation using a 2 × 2 factorial, open-label design. The study enrolled adult patients with severe sepsis or septic shock between 2003 and 2005 in 18 academic tertiary hospitals in Germany. Patients were enrolled if the onset of sepsis occurred less than 24 hours before admission to the ICU.

A factorial design may be used if 2 treatments that do not have any interaction (synergistic effect) are being evaluated. Thus patients are randomly assigned to 1 of 4 groups "treatment A and treatment Y," "treatment A and

treatment Z," "treatment B and treatment Y" and "treatment B and treatment Z." To compare treatment A and treatment B, the patients from both groups can be analyzed together. Similarly treatment Y and treatment Z can be compared using all patients. The benefit of such a design is that the sample size is much smaller than it would be if 2 studies were performed. In addition, it is possible to consider the separate effects of each intervention as well as the combined effect of both interventions. The risk of a factorial design is that if the 2 interventions are found to have an interaction, the presentation and interpretation of the results becomes very complex.

After the first planned safety analysis, the insulin therapy comparison of the trial was suspended owing to an increased rate of hypoglycemic events in the intensive insulin therapy group: 12.1% in the intensive insulin therapy group versus 2.1% in the conventional insulin therapy group ($p < 0.001$). When the trial was finally suspended after the enrollment of 600 patients, the rate of hypoglycemia in the intensive insulin therapy group was 17% (95% confidence interval [CI] 12.3–21.7) versus only 4.1% (95% CI 1.9–6.4) in the conventional insulin therapy group. Of note, the differences between the intensive and conventional insulin groups were found only for this outcome (safety outcome measure); there were no statistically significant differences in any of the efficacy outcomes.

At the time of trial suspension, patients in the HES group had a higher rate of acute renal failure (34.9% [95% CI 29.1–40.7] v. 22.8% [95% CI 17.8–22.8] in the Ringer lactate group). This translates into an absolute risk increase of 12.1% (95% CI 4.4–19.7) for acute renal failure in the HES group. In addition, they had a higher need for renal replacement therapy (31.0% [95% CI 25.4–36.7] v. 18.8% [95% CI 14.1–23.4] in the Ringer lactate group).

In this study, most patients were medical patients and 46.9% of patients ($n = 252$) had no history of surgery. The site of infection was most commonly the lungs (41.2%) followed by the abdomen (38.5%). The data were not analyzed by type of patient (surgical v. medical), but it is likely that the sample size would have been too small to draw meaningful conclusions. The data were also not analyzed by site of infection or by severity of sepsis (i.e., severe sepsis v. septic shock). Other specific treatment strategies that have been documented to impact on outcome in sepsis (e.g., adequacy of source control, timing and adequacy of resuscitation, appropriate antibiotic therapy) were not controlled in the VISEP study.

Despite these limitations, the VISEP study has highlighted the important issue of severe hypoglycemia with the use of intensive insulin therapy for tight glycemic control and demonstrated the potential nephrotoxicity of HES. Despite these results, the issue of tight glycemic control and choice of resuscitative fluid remain hotly debated.

The NICE-SUGAR trial,[4] published earlier this year is a randomized controlled trial involving more than 6000 patients comparing intensive (target blood glucose 81–108 mg/dL) versus conventional (target blood glucose ≤ 180 mg/dL) glucose control. In this study, mortality was increased in the intensive insulin therapy group. A meta-analysis that included the NICE-SUGAR trial data was also recently published[5] and showed an increased rate of hypoglycemic events in the intensive glucose control group, though the authors were unable to demonstrate an impact on mortality. Interestingly, a post-hoc cohort analysis of all surgical ICU patients did demonstrate a significant mortality reduction in the intensive glucose control group (relative risk 0.63, 95% CI 0.44–0.91; $n = 1972$).

The benefits of strict glycemic control in the ICU have not been established by either the VISEP or NICE-SUGAR trials. The choice of crystalloid versus colloid for fluid resuscitation also remains unanswered and will require further study. The VISEP study underlines the importance of publishing the results of negative trials. Although stopped prematurely, the study has given us important results that will help guide patient care and future study of both fluid resuscitation and glucose control in the septic patient.

Competing interests: None declared.

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