Canadian Association of General Surgeons Evidence Based Reviews in Surgery. 8. Efficacy and safety of recombinant human activated protein C for severe sepsis

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CAGS Evidence Based Reviews in Surgery

In September 2000, the Canadian Association of General Surgeons (CAGS) initiated a program entitled "CAGS Evidence Based Reviews in Surgery" (CAGS-EBRS) to help practising clinicians improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas. The *Canadian Journal of Surgery* will publish 4 of these reviews each year. Each review will consist of an abstract of the selected article and a summary of the methodologic and clinical reviews. We hope that readers will find these useful and learn skills that can be used to evaluate other articles. For more information about the CAGS-EBRS or information about participating in the program, send an email to mmckenzie@mtsinai.on.ca.

Selected article

Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344(10): 699-709.

Abstract

Objective: To find out whether activated recombinant protein C reduces the death rate from all causes at 28 days among patients with severe sepsis. **Design:** A randomized, double-blind, placebo-controlled trial. **Setting:** Multicentre; 164 centres in 11 countries. **Patients:** The study comprised 1690 patients (840 in the control group and 850 in the treatment group) who had known or suspected infection based on clinical data, plus 3 or more signs of systemic inflammation and sepsis-induced organ dysfunction for at least 24 hours. **Intervention:** Patients were randomized to intravenous infusion of drotrecogin α activated (24 µg/kg body weight hourly) for a total of 96 hours or placebo. **Main outcome measure:** Death from any cause at 28 days. **Results:** The death rate in the treatment group was 24.7% (95% confidence interval [CI] 22%–28%) and in the control group was 30.8% (95% CI 28%–34%). Treatment with activated protein C was associated with a reduction in the relative risk of death of 19.4% (95% CI 6.6%–30.5%) and absolute reduction in the risk of death of 6.1% (p = 0.005). Serious bleeding occurred in 3.5% of patients in the drotrecogin α activated group compared with 2.0% in the placebo group (p = 0.06). **Conclusion:** Treatment with activated protein C significantly reduces mortality (6.1% absolute reduction) with severe sepsis but may be associated with an increased risk of bleeding (treatment group 3.2%, p = 0.06).

Commentary

For several decades, the critical care literature has been plagued by an unfulfilled promise: to modulate the inflammatory response so as to

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improve patient survival. The latest candidate molecule is recombinant activated human protein C, an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation. After reported success in preclinical and phase 2 trials, the hypothesis tested in this article is that drotrecogin α (activated protein C) reduces the 28-day death rate from any cause among patients with severe sepsis.

The authors chose to include subjects with proven or suspected infection and a confirmed systemic inflammatory response severe enough to be classified as sepsis. The definition of sepsis in the classic sense is a systemic inflammatory response to invasive infection (bacterial, viral, parasitic). The majority of the infections in this study were confirmed or presumed pneumonias not the classic intra-abdominal "pus bellies" that general surgeons are faced with. For example, approximately 70% of the subjects in each group had no surgery, and in about 33% of patients, cultures were not obtained or gave negative results. Nevertheless, the acute physiology, age and chronic health evaluation II (APACHE II) scores were approximately 25, which indicates a significant degree of "illness." The authors stated that 75% of patients had at least 2 dysfunctional organs or systems at enrolment and three-quarters were on vasopressor support or were intubated.

At baseline, both groups appear remarkably well matched. In regard to the baseline patient characteristics, it is particularly important to study potential confounding factors with respect to the primary outcome as well as other outcomes. It is also important to see if key baseline descriptors have been omitted. In this case, for example, given the main medication side effect, the presence of a coagulopathy or a history of ulcers should have been described across groups.

The study patients were randomized to groups in a 1:1 fashion. Although the randomization method is not specified, there was a central randomization centre. Randomization was stratified by site, which is preferable in multisite trials, because this will balance centre-related effects. Although not specified here, recent trials use variable number blocks to further conceal randomization group. This technique is particularly useful if there is no placebo group or if the treatments have recognizable effects. For example, if the randomization blocks are known to be 4, an institution, which has randomized 2 patients to treatment, could predict that the next 2 patients would be randomized to placebo. The use of variable blocks effectively removes any ability to predict group assignment. In the study, 1728 patients were thus randomized into treatment and placebo groups. Seventeen patients in the placebo group and 21 in the treatment group never received placebo or drug. Most of the latter had at least 1 exclusion criterion, and all patients were ultimately accounted for. All patients but 1 were followed up for the full study period. This follow-up rate is to the investigators' credit, even though the study exhibited an unusually short end point of 28 days.

Details of efforts to conceal the allocation group after randomization are not clearly stated, but there is a suggestion that both study drug and placebo were dispensed in the same fashion to the treating team. There are also no data to suggest that a particular side effect may have led investigators to suspect the group to which patients had been randomized. Although serious bleeding might have suggested active treatment, thus compromising blinding, the overall prevalence of that side effect was low.

It is particularly important to question if both groups were treated equally because this is a very large multicentre trial where many different interventions may have been occurring in various centres, unknown to the study investigators. In fact, it is clearly stated that there was no standard treatment protocol for critical care patients in the trial. This decision can be argued, but is common in intensive care unit (ICU) trials dealing with a heterogeneous population. Standardization of treatment in both groups (other than the study medication) is most applicable to trials including patients with a single disease entity to ensure that effects measured are not related to a factor other than the experimental intervention (i.e., introducing a confounder). It is also more important when there is no placebo or if a particular side effect of the treatment medication compromises concealment. Nevertheless, one might have expected some standardization of the use of antibiotics. Recognizing this, to the authors' credit, a blinded clinical evaluation committee determined post hoc that appropriate antibiotics had been started within 48 hours of the diagnosis of severe sepsis in 91.3% of the treatment and in 91.2% of the placebo groups.

On intention-to-treat analysis, the observed mortality was 30.8% (95% CI 28%–34%) in the control group and 24.7% (95% CI 22%–28%) in the treatment group. The magnitude of mortality reduction in absolute terms is thus 6.1% (95% CI 2%–10%). The authors express this result as a reduction in relative risk of death (percent difference between groups/percent death in control group). These results hold true on Kaplan–Meier analysis and are duplicated in all predesignated subgroups of interest. Furthermore, the authors state that they had to stop the trial after an interim analysis had been conducted on 1520 patients, with survival favouring the treated patients.

Are these results statistically significant? Are they clinically significant?

The results are statistically significant because of the absence of

"zero" in the confidence interval around the difference in proportions of death between the groups. The "real" difference in mortality improvement, however, lies somewhere in the 95% CI between 2% and 10%. The clinical significance of the result is related to the "minimal difference" between the groups, which one would accept as being important to change one's practice. Arguably, in a case such as this, where mortality is the end point, any statistically significant improvement in mortality could be seen as an important finding. That might be true if there were not an underlying associated "cost." But there is always an associated cost, and hospitals or payers must decide if they are willing to pay it. For example, if the "true" improvement is close to 2%, but the cost of the drug prevents the purchase of much needed ventilators in the ICU, the opportunity of treating (and maybe saving) X% of other ICU patients would be "sacrificed" in exchange for this 2% improvement in mortality. Such a judgement is even more difficult to make if a whole city, region or country is considered. This promised benefit becomes even less clear if one finds fault with the primary outcome of a 28-day mortality. In this case, the chosen outcomes may be described as incomplete. Mortality usually relates to the ICU-based or total hospital-based episode of care. We have no information about what happened to patients after the 28-day study period. Indeed, the experimental medication may simply be delaying death to a later date without actually changing the death rate. This could insidiously lead to further increased costs owing to an actually prolonged, yet still fatal, hospitalization. Another point relates to the clinical significance of the "serious bleeding," which is not totally clear. For example, how many patients with intrathoracic bleeding ultimately require a thoracic decortication?

Nevertheless, any suspected reduction in mortality in such sick patients has been all but impossible to achieve with any previous "molecule." Moreover, there is no evident associated catastrophic side effect to the use of the study medication, although the associated bleeding requires further characterization. This is of particular importance to the practising general surgeon. Most surgical patients likely to benefit from this treatment are the ones with intra-abdominal infection due to perforated viscus with a major surgical procedure to control the source of the infection. Such patients are usually placed on broad-spectrum antibiotics and treated in the ICU. If they were to benefit from activated protein C, the drug should be administered immediately after the abdominal operation. The increased risk of bleeding, however, precludes this, and therefore the benefit of an absolute reduction of mortality of 6% may be attenuated, as the drug must be administered later in the septic course. Currently, activated protein C is not being widely used in Canada because of the cost, except in unusual circumstances where the company provides it. In the United States, the Federal Drug Administration has mandated more studies in patients with APACHE II scores less than 25 (the level of "sickness" below which the use of the drug may be questionable).

One last consideration remains, as in any drug-sponsored trial: whether the investigators had access to the raw data, performed the analysis independently and had control over the decision to publish. This has become an increasingly serious issue because of past negative experiences[1] and because large, highly publicized trials have become a central marketing tool.[2] A disclaimer does identify the authors as industry employees and their potential for a financial conflict of interest. There is, however, no accompanying statement relating the level of author independence or the level of support by the sponsor. The sponsor may have had very little involvement in the trial, but the burden of proof falls on the authors to communicate this, as suggested in a consensus statement by journal editors.[3] The issue of possible interference by the sponsor has gone from an issue of "competing loyalties" for the researcher to one of methodologic flaw similar to a lack of proper randomization or blinding, because it may introduce a significant bias.[1,4] However, the *New England Journal of Medicine* does not state whether it requires authors to sign a statement of independence from the sponsor or if the study protocol or contract review would have been made available upon request. In spite of these concerns, there does not appear to be any obvious suspicion of "foul play." Indeed, there is no suspicious exclusion of any centre, and no major outcomes appear to have been suppressed or downplayed.

Overall, the evidence appears to affirm the authors' claim of drug benefit. This is supported both by the biochemical evidence, which is congruous with the authors' initial hypothesis, and by the similarity of results in multiple "pre hoc" designated subgroups. The principal remaining question is whether this benefit is significant enough for us to afford it.

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