The term "evidence-based medicine" was first coined by Sackett and colleagues[1] as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding and it is impossible for an individual clinician to read all the medical literature. For clinicians to practice 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. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis and economics as well as clinical knowledge.

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsors a program entitled "Evidence-Based Reviews in Surgery (EBRS)," supported by an educational grant from Ethicon Inc and Ethicon Endo Surgery Inc. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website. A listserve discussion is held where participants can discuss the monthly article. Fellows and candidates of the College can access Evidence-Based Reviews in Surgery through the American College of Surgeons website (www.facs.org).

All journal articles and reviews are available electronically through the website. Currently we have a library of 50 articles and reviews which can be accessed at any time. Beginning in October, a new set of articles will be available each month until May. Surgeons who participate in the current (modules) packages can receive CME credits by completing a series of MCQ. For further information about EBRS the reader is directed to the ACS website or should email the administrator, Marg McKenzie at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the ACS and CAGS websites, 4 of the reviews are published in condensed versions in the *Canadian Journal of Surgery* and the other four will be published in the *Journal of the American College of Surgeons* each year.

REFERENCE

1. Evidence-Based Medicine Working Group. Evidence-based medicine. JAMA 1992;268:2420–2425.

SELECTED ARTICLE

Recombinant Factor VIIa Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

Boffard DK, Riou B, Warren B, et al, for the NovoSeven Trauma Study Group. J Trauma 2005;59:8–18.

Reviewed by

Karen Brasel, MD; John W Drover, MD; Brent Eastman, MD, for Members of the Evidence Based Reviews in Surgery Group.*

ABSTRACT

Question: Is recombinant factor VIIa (rFVIIa) effective as adjuvant therapy for controlling bleeding in patients with blunt or penetrating trauma?

Design: Two randomized placebo controlled, double blind trials (one in blunt trauma and one in penetrating trauma patients).

Setting: Thirty two hospitals in Australia, Canada, France, Germany, Isarael, Singapore, South Africa, and the United Kingdom.

Patients: Severely traumatized patients (defined as those physically injured and requiring 6 units of RBCs within 4 hours of admission) including 143 blunt trauma patients and 134 penetrating trauma patients.

Intervention: Patients in the intervention group received 3 injections of rFVIIa. The first intravenous injection was given immediately after the transfusion of 8 packed red blood cells (PRBC), and the second and third doses were given one and 3 hours after the first dose respectively. Patients in the control group received placebo injections.

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Main Outcome Measures: Primary outcome was the number of PRBC (autologous RBC, allogenic RBCs and whole blood) transfused during the first 48 hour period. Secondary outcomes were requirements for other transfusion products, mortality, days on ventilation, and days in the ICU.

Results: In the blunt trauma group the mean reduction (2.6 PRBC units, 90% CI p = 0.02) and the proportion of patients requiring massive transfusion (>20 units PRBCs) (14% vs 33% patients, 90% CI p = 0.03) were significantly decreased. In the penetrating trauma group there was a nonsignificant decrease in the mean reduction of the number of RBC transfused (mean 1.0, 09% CI, p = 0.10) and in the proportion of patients requiring massive transfusions (7% vs 19%, 90% CI, p = 0.08).

Conclusion: In blunt trauma patients, rFVIIa significantly reduces the need for RBC transfusion.

Commentary: Recombinant activated factor VIIa (rFVIIa) has been approved for use in the treatment of bleeding in hemophilia patients. Other studies have supported its use in the management of intracerebral hemorrhage. The initial use of rFVIIa in trauma was in the setting of military combat and since then off label use in both military and civilian settings has been reported. The optimal indications, dose, potential complications, and timing of this drug in blunt and penetrating trauma patients are not yet known. In the management of trauma associated coagulopathy, it is vital that adequate clotting factors and platelets are administered and that temperature, acidemia and hypocalcemia are brought toward normal. Once these factors are corrected, appropriate clotting within the host is more likely to occur. This point is emphasized by current recommendations for using a 1:1:1 (pRBCs: FFP: platelets) blood replacement strategy for hemorrhagic shock.

Boffard and colleagues performed two trials (one in blunt and one in penetrating trauma patients) to determine whether three doses of recombinant factor VIIa can reduce the 48-hour transfusion requirement for packed red blood cells in severely injured patients who require at least 8 units of blood during the first 4 hours of their treatment. Patients were randomized after admission to the hospital and after receiving 6 units of packed red blood cells. Treatment (study drug or placebo) was instituted after the eighth unit of packed red blood cells if the investigator believed that ongoing transfusion would be required. Two hundred micrograms of rFVIIa per kilogram was administered initially and two subsequent doses of 100 mcg/kg at 1 and 3 hours following the first dose. Treatment allocation was concealed from investigators and clinicians.

Three hundred one patients were enrolled and 277 patients were able to be evaluated. Eleven patients did not receive a total of 8 units of packed red blood cells and three patients died before administration of the investigational drugs, two patients were ineligible, one was withdrawn by the investigator, and consent for six patients could not be obtained.

Patients, clinicians, and study personnel were blinded to treatment. Treatment with recombinant factor VIIa affects coagulation parameters, however, monitoring of coagulation parameters was not part of the study, but there was no concealment of laboratory values, so investigators or treating clinicians could potentially have determined which treatment a patient received.

There were differences between the blunt and penetrating cohorts, but in each trial the two treatment groups were well-matched with respect to demographic, injury, and other treatment variables known to affect mortality, complications, and transfusion. In both trials young men predominated, although there were more men in the penetrating (94%) than in the blunt trauma cohort (70%). Patients < 16 years or > 65 years were excluded from the trial, as were patients with a Glasgow Coma Scale score < 8, pH < 7.0, transfusion of > 8 units packed red blood cells prior to hospital admission, base deficit > 15 mEq/L, injury > 12 hours before randomization, or cardiac arrest prehospital. Both cohorts were severely injured, with an average ISS of 32 in the blunt group and 26 in the penetrating cohort. Seventy seven percent of blunt-injured patients were injured in motor vehicle crashes; the majority of the remainder were injured in falls. Sixty eight percent of penetrating injuries were due to gunshot wounds, and the remainder were stab wounds. The mean initial hemoglobin was 9.2 g/dL in the blunt group and 8.6 g/dL in the penetrating group, with a mean pH of 7.25 in the blunt cohort and 7.28 in the penetrating group. In both trials, most patients were not hypotensive on arrival to the Emergency Department.

Clinical care was not altered although all sites developed massive transfusion protocols before the start of the study. The number of patients who required operative or angiographic hemorrhage control in each group was not reported. For these patients, time to the operating room and angiography suite are extremely important, and small differences can result in large differences in the

amount of blood and blood product resuscitation needed. Use of fresh frozen plasma and platelets were not restricted. The number of units transfused was not reported by group. This also has the potential to affect the amount of red blood cell resuscitation needed. Secondary endpoints included mortality, ventilator days, and critical care associated complications. Many of these complications are affected by care in the intensive care unit. The impact of subsequent care is so important that many trials have adopted accepted guidelines or protocols to minimize variation between clinicians and sites. Guidelines, most of which have been shown to decrease mortality or complications, exist for management of resuscitation (placement of a central venous catheter or pulmonary artery catheter), ventilatory strategies for ARDS, nutrition, management of hyperglycemia, and management of sedation.

The primary endpoint was initially defined as the number of units of packed red blood cells transfused in the first 48 hours. In addition, the number of units of packed red blood cells transfused in patients alive at 48 hours or more was analyzed. Mortality and clinically important complications were secondary endpoints. Thromboembolic events, a potential side effect from recombinant factor VIIa, were also monitored when they became clinically evident. Subclinical thromboembolic events were not monitored although they may be potentially relevant. Although no significant differences in thromboembolic events were found, others have found higher rates of thromboembolic complications in patients receiving factor VIIa.

In patients suffering blunt trauma, 48 hour transfusion requirement was significantly reduced by a mean of 2.6 units (90% CI 0.7–4.6, $p = 0.02$) in patients alive at 48 hours. In all blunt-injured patients, there was no significant decrease in the mean number of packed cells transfused at 48 hours (mean 2 U; 90% CI 0.0–4.6; $p = 0.07$). The proportion of patients requiring massive transfusion (>20 units packed red blood cells, including the initial 8 units prior to administration of study drug) in patients alive at 48 hours was significantly decreased from 33% to 14%, a relative risk reduction of 56%, (95% CI 9–79%; $p = 0.03$). This is a relatively large but fairly imprecise effect.

In patients with penetrating trauma who were alive at 48 hours, there was a nonsignificant reduction of, on average, one unit PRBC (90% CI 0–2.6; $p = 0.10$) in the first 48 hours ($p = 0.10$). In all penetrating trauma patients, the reduction was only 0.2 units of packed red blood cells (90% CI −0.9–2.4; $p = 0.24$). The proportion of patients alive at 48 hours who required massive transfusion was decreased from 19% to 7%, a relative risk reduction of 63% (95% CI −12–88%; $p = 0.08$).

The authors conclude that recombinant factor VIIa results in a significant reduction in pRBC transfusion in severe blunt trauma with a favorable safety profile. The evidence supporting the conclusion is weak because the basis for the conclusion is actually a modified primary endpoint (excluding all patients that died) rather than the a priori defined endpoint. In addition, the effect is extremely imprecise, weakening the strength of the conclusion. A recent European guideline for the management of bleeding after major trauma recommends that "the use of Recombinant Activated Coagulation Factor (rFVIIa) be considered if major bleeding in blunt trauma persists despite standard attempts to control bleeding and best practice use of blood components." This recommendation is given a 2C rating, a weak recommendation based on low or very low quality evidence.

There are several points related to the design of the study that are worth comment. First, informed consent prior to randomization was not required for this study, which was performed in Australia, Canada, France, Germany, Israel, Singapore, South Africa, and the United Kingdom. Investigators had the option of obtaining consent from the patient or a legally authorized representative. If neither were available, eligible patients were included in the study under waiver of informed consent guidelines. If this occurred, consent was obtained after the fact from either the patient or a legally authorized representative. If consent could not be obtained subsequently these patients' data were excluded from analysis. It is not clear whether ongoing data collection occurred. Research performed under waiver of informed consent is under close scrutiny in the United States, and it is unclear whether an in-hospital trial such as this could be conducted in the current United States climate.

Second, the sample size was calculated based on one sided alpha of 0.5. The authors argue that they used a one sided test because it was unlikely that rFVIIa would make the bleeding worse, which is a plausible assumption although use of a one-sided alpha is somewhat unusual. But while the results in the blunt trauma group were statistically significant based on a one sided test, they would not be statistically significant if a two sided

test were performed. Similarly, 90% CI were calculated because one sided test was used, but if 95% CI were calculated the range would have been wider and crossed one.

Third, the primary outcome is analyzed in patients alive at 48 hours. While the authors make a strong argument for this, trialists always have concern when an intention to treat (ie, analysis of all randomized patients) analysis is not the primary one. If this were the case in this trial, the differences would not be statistically significant. If the primary analysis was to be based on patients alive at 48 hours, then the authors should have adjusted their sample size. Despite calculating a sample size of 140 patients only 117 in the blunt trauma trial and 112 in the penetrating trauma trial were evaluable.

Finally, it should be noted that the study was funded by Novo Nordisk. Four of the authors received personal funding from Novo Nordisk and one author is a former employee of Novo Nordisk. The role of the sponsoring company is not stated.

In conclusion, the efficacy of rFVIIa has not been proven. This is an expensive weapon in our arsenal against bleeding, and we have yet to define patient selection criteria and delineate the risks associated with what is possibly a very effective drug when used correctly. Although appropriate for individual trauma patients with life-threatening hemorrhage, its role in the population of critically injured patients in hemorrhagic shock or with intracerebral hemorrhage is unclear.