



## New Frontiers in SURGERY

### Hemostatic Therapy Advances in Trauma and Surgery

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**Calgary** - Major bleeding substantially increases patient risk in any clinical situation, regardless of whether it is the primary problem as in hemophilia or secondary to surgery or traumatic injury. Options for controlling bleeding remain fairly limited. Surgery, mechanical embolization (in selected clinical situations) and blood products constitute mainstream therapy. Alternatives to these three basic approaches have begun to emerge. Antifibrinolytics, such as aprotinin and lysine analogues, have proven useful in some circumstances. More recently, recombinant factor VIIa (rFVIIa) has emerged as a potential option for managing major bleeds. Used for more than a decade in the treatment of hemophilia with inhibitors, it is being evaluated in a variety of non-hemophilia conditions, including intracerebral hemorrhage, major surgery and trauma.

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Major bleeding in trauma patients is an especially critical issue, noted Dr. Sandro Rizoli, Assistant Professor of Surgery and Critical Care Medicine, University of Toronto, Ontario. Trauma-associated problem bleeding makes the largest single contribution to use of blood products and is the leading cause of mortality during the first 48 hours after hospital admission (Sauaia et al. *J Trauma* 1995;38(2):185-93).

#### Managing Major Bleeds: A Priority

As emphasized more than a decade ago in a large randomized study evaluating fluid resuscitation in hypotensive trauma patients, the first priority in the management of a major bleed is to stop the bleeding (Bickell et al. *N Engl J Med* 1994;331(19):1105-9). The results showed that patients who received usual care, including large quantities of fluids, actually had a lower survival than did patients who received minimal fluid replacement during acute management. "Many people mistakenly believe this was a study about fluid," remarked Dr. Rizoli. "This was a study about bleeding,

and the results showed that the absolute priority is managing large bleeds in trauma patients."

A second priority in managing major trauma-associated bleeding is to control the underlying coagulopathy by restoring the patient's clotting factors. Historically, the strategy comprises four interventions: red blood cells (RBC) until hemoglobin (Hb) >70 g/L; fresh frozen plasma (FFP) until international normalized ratio (INR) <1.5; platelets >50,000; cryoprecipitate until fibrinogen >1 g/L.

Unfortunately, this strategy has minimal scientific or clinical basis, noted Dr. Rizoli. In the case of cryoprecipitate, for example, the recommendation for trauma patients is based entirely on case reports.

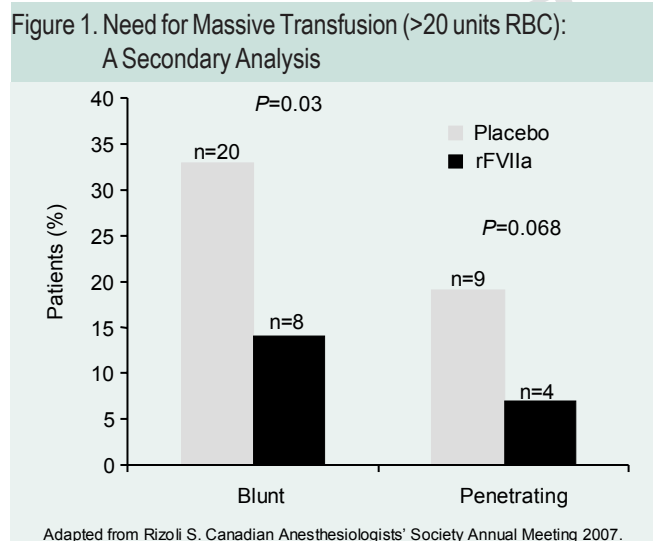
In the absence of good laboratory support, the empiric approach to resuscitation has been to give 8 U of RBC, followed by 4 U of FFP and 5 U of platelets. Recent field experience related to the military conflict in Iraq suggests that a more appropriate approach would be to withhold crystalloids and resuscitate with 16 U of blood, followed by FFP, platelets and RBCs given in a 1:1:1 ratio

(Hess et al. *Transfusion* 2006;46(5):685-6, Holcomb et al. *J Trauma* 2007;62(2):307-10).

### Hemostatic Treatment in Trauma Patients

The need for better approaches to management of major bleeding in trauma patients has led to an examination of new hemostatic agents, including recombinant factor VIIa (rFVIIa). Consequently, the agent was evaluated as adjunctive therapy for bleeding control in two parallel, randomized, placebo-controlled clinical trials of severely injured trauma patients (Boffard et al. *J Trauma* 2005;59(1):8-15). The trials produced some curious results, observed Dr. Rizoli, a co-investigator in the studies.

Use of rFVIIa in addition to standard care significantly reduced the need for RBC transfusion ( $\geq 8$  U) ( $P=0.02$ ) and for massive transfusion ( $>20$  U) ( $P=0.03$ ) in patients with bleeding secondary to blunt trauma but not penetrating trauma (Figure 1).



A separate analysis showed that coagulopathic patients who received rFVIIa needed significantly fewer RBC units, FFP and platelets compared to placebo-treated patients. “I don’t understand why factor VIIa didn’t make a difference in patients with penetrating trauma,” remarked Dr. Rizoli. “The data on coagulopathic patients showed that it works.”

Investigators at the University of Toronto and Sunnybrook Medical Centre carried out their own evaluation of rFVIIa in trauma patients. They identified 319 patients who had received  $>8$  U of RBC in the first 12 hours, 60 of whom were treated with rFVIIa. A multivariate analysis showed that patients who received rFVIIa had a fourfold greater 24-hour survival and a threefold greater overall survival.

On the basis of available data, Dr. Rizoli and colleagues in Toronto administer rFVIIa to patients who have persistent bleeding related to blunt trauma despite receiving 8 U of RBC. Patients with penetrating injuries receive the agent only if they are coagulopathic.

### Hemostasis in Spinal Surgery

The need for better control of hemostasis in spinal surgery has led to examination of rFVIIa as add-on therapy, indicated Dr. Serena Hu, Professor of Orthopaedic Surgery and Chief, Spine Service, University of California, San Francisco. She briefly discussed a recently completed phase II randomized clinical evaluation of rFVIIa in patients undergoing major spinal surgery. The data could not be presented in detail because of pending publication.

Patients enrolled in the trial were randomized to 30, 60 or 120  $\mu\text{g}/\text{kg}$  of rFVIIa or placebo in addition to usual care. The primary objective of the study was the safety of rFVIIa in this patient population. Secondary objectives included the per cent blood loss and its impact on blood loss. The trigger for initiation of rFVIIa was 10% loss of estimated blood volume, and treatment was repeated two and four hours later.

“We think that estimated blood loss offers a good model for evaluating prothrombotic agents,” Dr. Hu concluded. “We found factor VIIa safe at the highest dose tested. There were no significant adverse events in patients who received the highest dose. We don’t know what is the optimal dose for spine patients, and these results suggest a need to test lower doses.”

### Preventing Blood Loss and Early Management of Blood Loss in Cardiac Surgery

The discussion of hemostatic therapies concluded with a presentation on identification of coronary bypass patients at risk for massive blood loss, defined according to the following: replacement of 100% blood volume in 24 hours; replacement of 50% of blood volume in three hours; transfusion of 10 U RBC within 24 hours; transfusion of 4 U RBC within one hour when ongoing need is foreseeable (Wojciechowski et al. *Int Anesthesiol Clin* 2005;43(4):1-20).

A fifth factor used to define massive blood loss was acute transfusion of 5 U or more of RBC, a standard used by Dr. Keyvan Karkouti, Assistant Professor of Anesthesia and Clinical Epidemiology, University of Toronto, Ontario, and colleagues. Between 15% and 20% of patients at Canadian hospitals require massive blood transfusions by the definition used at Toronto General Hospital, according to data in press, noted Dr. Karkouti.

Massive blood loss (or transfusion) correlates with an increased risk of adverse events and is independently associated with mortality. A scoring system developed by Dr. Karkouti and colleagues is used to accurately identify patients who have a high risk for massive blood transfusion (Karkouti et al. *Can J Anaesth* 2006;53(8):781-94). Factors that increase risk include older age, preoperative shock, preoperative hemoglobin and platelet count, complexity of the procedure, hematocrit nadir, body surface area, redo surgery, circulatory arrest, and time on cardiopulmonary bypass machine.

Early management of bleeding in patients at risk of massive blood loss comprises a seven-pronged approach in avoiding hypovolemia, hypothermia, acidosis, hypocalcemia, anemia, dilutional coagulopathy and administering hemostatic drugs.

Administration of antifibrinolytic agents offers another strategy to minimize the risk of massive blood loss, remarked Dr. Karkouti. Aprotinin has demonstrated the ability to reduce the number of transfusion units in patients undergoing repeat coronary artery bypass graft (CABG) surgery. However, antifibrinolytics do not work in every patient. About 30% of CABG patients require 5 U or more of RBC despite antifibrinolytic therapy, and 10% require 10 U or more of RBC (Karkouti et al. *Transfusion* 2006;46(3):327-38). In very high-risk patients, about 60% require 5 U or more of RBC and almost 30% require 10 U or more.

Use of antifibrinolytics is complicated by the fact that physicians have more than one therapeutic option. Aprotinin, which has been extensively evaluated in randomized controlled trials, works by inhibiting serine proteases. Tranexamic acid, a lysine analogue, blocks the binding of plasminogen and endogenous tissue plasminogen activator to fibrin. Aprotinin is considerably more expensive than tranexamic acid, which has not been evaluated clinically to the same extent as aprotinin (Mannucci PM, Levi M. *N Engl J Med* 2007;356(22):2301-11).

Recent reports have raised questions about the safety of aprotinin, noted Dr. Karkouti. The agent has been associated with an increased risk of adverse events, including renal dysfunction and failure, stroke, myocardial infarction, and increased short- and long-term mortality (Mangano et al. *N Engl J Med* 2006;354(4):353-65, Mangano et al. *JAMA* 2007;297(5):471-9). In a recent comparison of aprotinin and tranexamic acid, Dr. Karkouti found aprotinin was associated with an increased risk of renal dysfunction, but not other adverse events (Karkouti et al. *Transfusion* 2006).

A meta-analysis of placebo-controlled trials of antifibrinolytic agents showed that all reduce blood loss compared to placebo in patients undergoing CABG (Brown

et al. *Circulation* 2007;115(22):2801-13). The various agents had comparable effects on the risk of stroke, mortality, myocardial infarction and renal failure. However, high-dose aprotinin was associated with a statistically significant increased risk of renal dysfunction compared to the other antifibrinolytics.

Dr. Karkouti stated that prophylactic rFVIIa has been evaluated in randomized controlled trials of non-coagulopathic and coagulopathic patients undergoing major surgery. Collectively, the trials have demonstrated minimal efficacy but no safety concerns. However, problems with the design of those studies leaves the issue unresolved.

Case-control data on rescue use of rFVIIa has produced evidence suggesting efficacy but possibly an increased risk of adverse events. Dr. Karkouti and colleagues recently reported findings from 114 consecutive patients who received rFVIIa for refractory bleeding after cardiac surgery (Karkouti et al. *Can J Anaesth* 2006;53(8):802-9). Outcomes in those patients were compared with outcomes in 541 patients with excessive but non-refractory blood loss. After adjustment for differences in baseline risk, the analysis revealed a statistically significant reduction in the risk of adverse events in those who received rFVIIa early vs. late (after blood loss of 8 U).

“This is just hypothesis-generating data at this point, but it is an interesting finding. Whether early administration [of rFVIIa] reduces the risk of adverse events remains to be seen,” concluded Dr. Karkouti.

### Questions and Answers

The following question-and-answer session is based on an interview with Dr. Sandro Rizoli, Assistant Professor of Surgery and Critical Care Medicine, University of Toronto, Ontario.

**Q:** *Have clinical studies conducted thus far ruled out a role for prophylactic use of rFVIIa in patients undergoing major surgery?*

**A:** No, they have not ruled out this possibility but most studies to date have failed to demonstrate benefit when rFVIIa is used to reduce or prevent blood loss during surgery, which is a fascinating possibility. The best clinical studies on the use of rFVIIa as a prophylactic agent demonstrating no benefit include a double-blinded randomized controlled trial (RCT) in patients undergoing reconstruction surgery for pelvic fracture (Raobaikady et al. *Br J Anaesth* 2005;94(5):586-91), two RCTs in liver transplantation (Planinsic et al. *Liver Transpl* 2005;11(8):895-900, Lodge et al. *Liver Transpl*

2005;11(8):973-9) and one RCT in liver resection (Shao et al. *Am J Surg* 2006;191(2):245-9). On the other hand, even though an RCT in elective prostatectomy published in 2003 concluded that rFVIIa significantly reduces intra-operative blood loss and the need for blood transfusion, rFVIIa remains infrequently used for prophylaxis in elective prostatectomy (Friederich et al. *Lancet* 2003;361(9353):201-5). An area that seems to benefit from the prophylactic use of rFVIIa is spinal surgery. A European retrospective study in patients undergoing elective surgery for scoliosis demonstrated a significant reduction in intra-operative blood loss and need for transfusion (Kolban et al. *Eur Spine J* 2006;15(6):944-52). Larger studies, including an RCT recently completed, are expected to support the concept that rFVIIa has a role as a prophylactic agent in spinal surgery. For now, the best use of rFVIIa seems to be in the management of large and often refractory perioperative bleeding.

**Q: You suggested administering this hemostatic agent to manage large bleeds in trauma “not as a last resort.” In your opinion, when would the optimal time be?**

**A:** The optimal time to administer rFVIIa to a bleeding traumatized patient has not been definitively determined. The best evidence guiding the time of administration is the RCT published in 2005 (Boffard et al. *J Trauma* 2005). In this large RCT, rFVIIa was administered after 8 U of RBC was transfused—about the time the patient’s whole blood volume was replaced once. Many experts consider 8 U of RBC to be “too late” and currently administer rFVIIa to bleeding trauma patients receiving 4 to 8 U of RBC (Vincent et al. *Crit Care* 2006;10(4):R120). In Iraq and Afghanistan war zones, where blood products may be scarce, rFVIIa is administered at arrival to the hospital to

bleeding patients with an INR  $\geq 1.5$  (verbal communication). In my opinion, for the physician practicing in non-war zones, it is best to make the decision on when to use rFVIIa based on available evidence, so about the time of the eighth unit of RBC. In my opinion, using after 8 U is “too late,” but certainly not contraindicated. The strongest contraindication to rFVIIa is to use it as “last resort,” or when everything else fails. The reason being that these patients are unsalvageable and the drug is unlikely to be of any benefit. An excellent study on the futility of using rFVIIa as a “last resort” has been published (Clark et al. *Vox Sang* 2004;86(2):120-4).

**Q: At this point, what is the best established clinical application of rFVIIa in surgery?**

**A:** The best evidence demonstrating benefits to surgical and/or critical care patients are in trauma and cardiac surgery. In trauma, a large RCT demonstrated that rFVIIa significantly reduces the need for blood transfusion in blunt trauma, when the patient becomes coagulopathic or when requiring massive blood transfusions. In cardiac surgery, rFVIIa has been shown to reduce blood transfusion and need for re-operations particularly in massive and refractory post-operative bleeding. Weaker evidence, based mostly on case reports, suggests that rFVIIa is a beneficial therapy in the management of large post-operative bleeding (general, orthopedic, urological, gynecological, vascular and most surgical specialties) and postpartum. Published guidelines best summarize the proven indications for rFVIIa including European guidelines (Vincent et al. *Crit Care* 2006) and Israeli guidelines (Martinowitz et al. *J Thromb Haemost* 2005;3(4):640-8). Another good review on rFVIIa in surgery has also been published by Scarpelini et al. (*Curr Opin Crit Care* 2006;12(4):351-6). □

Note: At press time, in Canada, recombinant factor VIIa is indicated in hemophilia A/B patients with inhibitors to FVIII or FIX for the treatment of bleeding episodes.

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