



Pathophysiology of Bleeding in Surgery

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ABSTRACT

Bleeding is a major surgical complication. Although mortality rates of 0.1% are observed for surgical procedures, it may be 5% to 8% for elective vascular surgery, and increase to 20% in the presence of severe bleeding. In major surgery for liver diseases, as well as in cardiac surgery, excessive blood loss is associated with increased mortality, morbidity, and intensive care stay. Approximately 75% to 90% of intraoperative and early postoperative bleeding is due to technical factors. However, in some cases either acquired or congenital coagulopathies may favor, if not directly cause, surgical hemorrhage. Uncontrolled bleeding leads to a combination of hemodilution, hypothermia, consumption of clotting factors, and acidosis, which in turn worsen the clotting process, further exacerbating the problem in a vicious bloody circle. At present, the standard treatment for surgical bleeding is the rapid control of the source of bleeding by either surgical or radiological techniques. Blood-derived products as well as hemostatic agents, such as aprotinin, tranexamic acid, and DDAVP, are widely used to improve hemostatic balance in bleeding patients. Recombinant activated factor VII (rFVIIa) has been reported to be effective for the treatment of surgical or traumatic massive bleeding unresponsive to conventional therapy. Although most reports are anecdotal, and therefore exposed to a "positive" selection bias, the number of cases is impressive, strongly suggesting that in such patients rFVIIa may afford a hemostatic advantage beyond that of conventional replacement therapy.

BLEEDING is a potential complication of any surgical procedure, representing a major challenge for the surgeon and the anesthetist. The larger and more complex the surgery, the greater the potential for unexpected severe bleeding. Although mortality is low for most surgical procedures, ranging from less than 0.1% for most routine surgery to 1% to 2% for cardiac surgery and 5% to 8% for elective vascular cases, the low mortality may be greatly increased when severe bleeding occurs during the operative procedure. Severe, unexpected, and uncontrollable bleeding during the operation can raise the mortality rate from <1% to 20%, an observation reflected in most surgical scoring systems that predict outcome, such as POSSUM¹ and TRISS.²

Major surgery for liver diseases, such as partial hepatectomy and orthotopic liver transplantation (OLT), is associated with significant blood loss, although most transplant centers now report half the use of blood products compared to 10 years ago. Nevertheless, excess blood loss remains an important issue, as it is associated with increased morbidity, mortality, and intensive care stay.³

Cardiac surgery is also often associated with profuse hemorrhage. Excessive bleeding (>2 L after surgery) is encountered in 5% to 7% of patients. It may require re-operation in 3.6% to 4.2% of patients if conventional methods fail to arrest the bleed.^{4,5} Clinical experience and observational studies demonstrate that massive blood loss is linked to adverse outcomes. It is associated with an eightfold increase in the odds of death.⁶

But why do surgical patients actually bleed? It could be easy, and perhaps too easy, to answer: "Because of surgery itself." Indeed, the most common cause of significant intraoperative bleeding is inadequate surgical hemostasis, the so-called silk deficiency. Nearly all reviews of intraoperative and early postoperative bleeding point out that 75%

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Table 1. Causes of Intraoperative and Postoperative Hemorrhage

Intraoperative
Structural/technical defects
Disseminated intravascular coagulation
Heparin overdose
Hyperfibrinolysis
Early postoperative (days 0–2)
Structural/technical defects
Thrombocytopenia
Inherited or acquired platelet disorders
Mild to moderate inherited coagulation disorder
Delayed postoperative (days 2–7)
Thrombocytopenia
Acquired platelet disorders (aspirin or NSAID)
Vitamin K deficiency
Multiorgan failure
Antibodies to factor V following use of bovine thrombin in fibrin glue

to 90% of all bleeding is technical in nature.⁷ Moreover, it has been demonstrated that surgical technique per se affects the rate of postoperative hemorrhage.^{8,9} However, as Table 1 shows, in some cases either acquired or congenital coagulopathies may at least favor, if not directly cause, surgical bleeding. Whatever the cause, uncontrolled bleeding can lead to a combination of hemodilution, hypothermia, consumption of clotting factors, and acidosis, which in turn exert their own negative influences over the clotting process to further exacerbate the problem in a vicious bloody circle¹⁰ (Table 1).

Dilutional thrombocytopenia represents the most common of the coagulation abnormalities occurring in patients with heavy bleeding. It is particularly common among those receiving transfusion volumes in excess of 1.5 times their blood volume.¹⁰ After replacement of one blood volume, only 35% to 40% of platelets remain in the circulation. Moreover, dilution of procoagulant factors is an acknowledged feature of fluid resuscitation, occurring as a result of transfusion of packed red blood cells or crystalloid solutions.

The severely bleeding patient faces a high risk of developing *hypothermia*, which adversely affects coagulation, as it causes platelet dysfunction, alteration of coagulation enzyme kinetics, disruption of fibrinolytic balance, and prolongation of clotting time.¹¹ It has been demonstrated that at a temperature of 33°C the impairment in coagulation processes is equivalent to a factor IX deficiency of 33% of its normal level, a situation that perhaps may be named “B hemophilia.” Moreover, a greater degree of clot lysis, attributed to the impairment of intrinsic inhibitors of fibrinolysis such as PAI or $\alpha 2$ antiplasmin, occurs at lower temperatures.¹¹

Tissues damaged from surgery release thromboplastin (ie, tissue factor), which causes intravascular activation of coagulation and thrombin formation. If coagulation activation exceeds the physiological inhibitory capacity, a profile

of disseminated intravascular coagulation develops, characterized by *systemic clotting factor depletion* and enhanced fibrinolysis, leading to a diffuse coagulopathy.

Massive hemorrhage eventually results in intracellular derangements in oxygen and substrate utilization that lead to *metabolic acidosis*. Studies have demonstrated a strong correlation between the development of coagulation abnormalities and the duration of hypotension. It has also been demonstrated that hypoperfusion is associated with consumptive coagulopathy, prolongation of APTT, and decreased factor V activity with microvascular bleeding.¹⁰

At present, the standard treatment for significant hemorrhage during surgery is the rapid control of the source of bleeding by one of the following methods: surgical techniques; packing or tamponading the area; ligation of major vessels leading to the bleeding area; radiological intervention to thrombose the vessels leading to the bleeding area; and the use of blood-derived products, such as platelets, fresh frozen plasma (FFP), and cryoprecipitate. The action of these products may be enhanced by the use of fibrin sealants and other pharmacological agents, such as aprotinin, tranexamic acid, and DDAVP. Despite these interventions, there still remains a need for an agent that will enhance local hemostasis, ideally devoid of any thrombotic effect.

The literature offers now a rapidly growing body of case reports strongly suggesting that rFVIIa should be considered to be an effective and safe adjunctive hemostatic treatment for severe bleeding unresponsive to conventional therapy.

Initiation of hemostasis involves the formation of a complex between tissue factor (TF) and activated factor VII (FVIIa) following injury. In physiological conditions, TF is found in the subendothelium. It is only exposed to the circulating blood after tissue damage, although it can be expressed by several types of cells as a consequence of thrombogenic stimuli. The complex TF–VIIa then activates both factors IX and X, and catalyzes the auto-activation of more FVII.¹² This chain of events is now known to be the main physiological pathway leading to the hemostasis in vivo. On these grounds, recombinant activated FVII (rFVIIa) has been widely used for the treatment of bleeding episodes in patients affected by either congenital or acquired coagulopathies.¹³ Moreover, the powerful prohemostatic activity of rFVIIa has prompted some investigators to use it after failure of conventional hemostatic measures in patients experiencing massive bleeding following trauma or surgery.^{14,15} In contrast to the growing realization that rFVIIa can be considered to be a universal and powerful hemostatic agent, many unanswered questions remain about the timing of administration, the optimal dosing regimen, and the safety profile. All these questions must be addressed by solid, well-designed clinical trials.

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