

SECTION II. THERAPEUTIC STRATEGIES

Surgical Perspectives to Control Bleeding in Trauma

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Learning Objectives: 1) To specify mechanisms of hemostasis following injury. 2) To understand operating room priorities for hemorrhage control in the treatment of the injured patient. 3) To discuss use of topical hemostatic agents, advanced hemostatic dressings, and recombinant activated factor VII in clinical practice.

Abstract

Only a secure airway and optimum oxygenation/ventilation are higher priorities than hemorrhage control following injury. The purpose of this article is to examine (1) normal hemostasis and the pathophysiology of coagulation following injury, (2) general management principles and operating room priorities, (3) data on topical hemostatic agents, advanced hemostatic dressings, and recombinant activated factor VII, (4) unique patient populations, and (5) the use of specific interventions to control hemorrhage in current clinical practice.

Significance of Hemorrhage

After establishing a secure airway and ensuring adequate oxygenation and ventilation, the highest priority in the management of the injured patient is to control hemorrhage. Because patients may bleed from multiple sites simultaneously, it is imperative that a strategy be devised to identify and control all possible sources of hemorrhage. Hemorrhagic shock, which accounts for 30% to 40% of injury-related fatalities, is the second leading cause of death overall and the most frequent cause of death within 1 hour following injury.¹⁻⁴ Nicholas et al⁵ found that, in patients with penetrating abdominal trauma, 79% of deaths occurred within 24 hours because of hemorrhage. Of patients who die in the operating room after injury, bleeding is causative in 82%.⁶ Lack of hemorrhage control accounted for 28% of fatal management errors in one mature trauma program.⁷ The control of hemorrhage is a multidisciplinary endeavor involving trauma surgeons, orthopaedic surgeons, radiologists, and anesthesiologists. This article examines the physiology of coagulation and addresses methods to control bleeding in the injured patient.

Hemostasis

Hemostasis is the means by which blood loss is terminated from an injured artery or vein. The process uses circulating proteins, cellular elements, and the endothelial lining (Figs. 1 and 2).⁸ The first response to injury is vasoconstriction, which involves responses brought on from direct injury to the blood vessel wall, circulating catecholamines, and local mediators. Circulating platelets, exposed to subendothelial collagen, quickly adhere to each other and the blood vessel wall. von Willebrand factor facilitates adhesion by acting as a bridge between the exposed subendothelium and the platelet membrane, where it binds to receptor sites made available as a result of platelet activation. Other platelets are then recruited from the blood, forming a loose plug that seals the blood vessel. If this response reaches sufficient intensity, the platelet release reaction occurs whereby the contents of platelet granules are liberated into the surrounding microenvironment. This is a complex reaction involving adenosine diphosphate, serotonin, platelet factor,⁴ platelet-derived growth factor, thrombin, calcium, and magnesium.^{8,9} The result is formation of a stable platelet plug, which, unlike the initial loose plug, will not dissolve spontaneously.

Platelet reactions occur simultaneously with events of the coagulation cascade. There are two traditional divisions of the coagulation process: the intrinsic system and the extrinsic system.⁸ The intrinsic system is initiated by the interaction of factor XII and nonendothelial surfaces, which induces a conformational change in factor XII. The reactions that follow lead to clotting, kinin formation, complement activation, and fibrinolysis.⁸ The release of plasminogen activator from injured endothelium and activation of factor XII initiates fibrinolysis simultaneously with the clotting cascade. These reactions convert plasminogen to plasmin, which can digest fibrin and fibrinogen at the site of clotting, limiting the hemostatic response to the area of injury and maintaining vascular

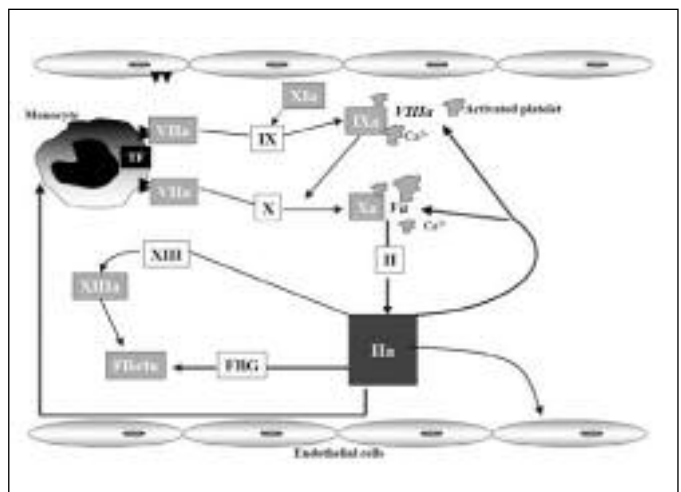


Figure 1. Activation of the coagulation system. The initiating event for coagulation is exposure of tissue factor (TF) to FVII and circulating trace amounts of FVIIa. The TF-FVIIa complex activates FIX and FX, generating low amounts of FXa. FBG, fibrinogen; IIa, thrombin. (From Lasne D, et al. From normal to pathological hemostasis. *Can J Anesth* 2006;53(6):S2-S11, with permission.)

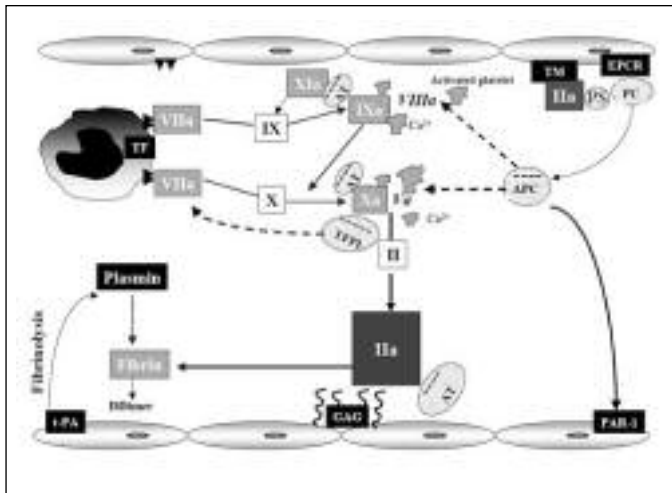


Figure 2. Regulation of hemostasis. After an initial triggering event, sequential steps occur, including a complex cascade of clotting factor and platelet activation. The three distinct phases of hemostasis are (1) primary hemostasis, (2) coagulation, and (3) fibrinolysis. Regulating factors such as antithrombin (AT), protein C (PC), protein S (PS), and tissue factor (TF) inhibitor are synthesized by the liver. Proteins C and S are vitamin K-dependent factors. The so-called intrinsic pathway plays a minor role in physiologic hemostasis. TFPI, tissue factor pathway inhibitor; APC, activated protein C; EPCR, endothelial protein C receptor; TM, thrombomodulin; GAG, glycosaminoglycan; PAR-1, protease-activated receptor 1. (From Lasne D, et al. From normal to pathological hemostasis. *Can J Anesth* 2006;53(6):S2-S11, with permission.)

patency. A complex inhibition system inactivates any plasmin that gains access to the general circulation.

The extrinsic system is the more important hemostatic sequence following trauma. Tissue thromboplastin (tissue factor) is expressed by subendothelial cells (smooth muscle cells and fibroblasts) in response to tissue trauma. When tissue factor is present, factor VII becomes activated and the sequence ensues. The two systems merge into a common pathway with the activation of factor X, which converts prothrombin to thrombin. Fibrinogen is then acted on by thrombin, resulting in the formation of fibrin monomers. Polymerization of the fibrin monomers results in a cross-linked, stable, fibrin clot.

General Management of the Bleeding Patient after Injury

There must be a rapid and thorough search of the five possible locations for blood loss following injury (Table 1). The clinical pathophysiology of hemorrhage is made manifest by tachycardia, hypotension, oliguria, and decreased mental status. Aggressive means must be taken to stop blood loss and reverse hypotension in order to prevent acidosis, coagulopathy, and hypothermia. Increasing depth and duration of hypotension has been shown to be significantly associated with mortality.¹⁰ Worsening base deficit results in statistically greater transfusion volumes, coagulopathy, and organ dysfunction.¹¹ Clot formation time in healthy volunteers is significantly impaired by acidosis and the effects are reversed by buffering.¹² Hypothermia also prolongs clotting times and causes platelet dysfunction.¹³ In trauma patients, abnormal initial prothrombin time (PT) or activated partial thromboplastin time assays are significantly associated with mortality.¹⁴

Table 1. Blood Loss in Trauma

Site	Potential Volume
External (roadway or floor)	Exsanguination possible
Thorax	Greater than 1.5 L per hemithorax
Peritoneal cavity	Exsanguination possible
Pelvis and retroperitoneum	Exsanguination possible
Long bone fractures	Tibia/humerus, 750 mL; femur, 1,500 mL

Coagulation factors are lost from circulation, consumed by coagulation, and exhibit reduced activity because of hypothermia, acidosis, and dilution with asanguinous fluid.¹⁵ Prophylactic administration of fresh-frozen plasma (FFP) or platelets in the absence of clinical bleeding is not warranted.^{16,17} However, there is a growing emphasis on the need for earlier use of FFP before coagulation factors decline to critical levels in patients with significant bleeding.^{15,18,19} With ongoing bleeding in severe trauma, FFP and packed red blood cells (PRBCs) should be administered in a 1:1 ratio.^{18,19} It is easy to “get behind” in this process, because it takes 20 to 30 minutes for FFP to thaw before administration. The platelet count should be kept at a minimum of 50,000 per microliter.^{15,19,20} Although overall mortality from massive transfusion is in excess of 70%, survival has increased over the past decade because of advances in surgical technique, rewarming, coagulopathy correction, and improved blood banking.²¹

General Priorities in the Operating Room

At laparotomy (or any operation following injury) it is absolutely necessary to control hemorrhage in the most rapid fashion possible. Dr. William Halsted considered this essential for all types of surgery and eloquently stated the rationale²²: “*The confidence gradually acquired from masterfulness in controlling hemorrhage gives to the surgeon the calm which is so essential for clear thinking and orderly procedure at the operating table.*”

After hemorrhage is controlled, gastrointestinal contamination is next addressed (Table 2). Only after these goals are accomplished can a thorough exploration of the abdomen be carried out and all injuries dealt with definitively. The patient’s general condition, however, may not allow all injuries to be addressed fully at initial exploration. The “bloody vicious cycle” (coagulopathy, hypothermia, and metabolic acidosis) should compel the trauma team to use a damage control approach.^{23,24} The primary objectives of damage control are to arrest bleeding, limit gastrointestinal contamination, and enclose the abdomen to protect viscera and limit protein loss.²⁴ Subsequent operations are required to remove laparotomy sponges used for tamponade, restore gastrointestinal continuity if required, and to attempt abdominal wall closure when the patient’s condition is more acceptable. Rotondo et al²³ showed that in patients with major vascular injury and two or more visceral injuries, damage control improved survival. Damage control principles, including packing, have been used in the thorax with no significant elevations in airway pressure.²⁵ Damage control orthopaedics, using external fixation, reduces operative time and blood loss, and does not hinder definitive osteosynthesis conversion.²⁶

Table 2. Operating Room Priorities for the Injured Patient

1. Control of hemorrhage
2. Stop gastrointestinal contamination
3. Replace coagulation factors
4. Maintain normothermia and acid-base balance
5. Thorough exploration of abdomen (or other site of injury) if condition permits
6. Temporary abdominal closure if there is significant visceral edema
7. Timely transfer to intensive care unit for continued resuscitation
8. Subsequent operations if required

There are many tools used for hemorrhage control following injury. The most obvious is the application of digital pressure. Although not definitive control for large vessels, the surgeon’s finger is the most atraumatic instrument available and will control bleeding temporarily while the blood vessel is exposed to allow for repair or ligation. Occasionally, one may need to gain control of the aorta at the diaphragmatic hiatus while exposure is accomplished in order for the anesthesiologist to replace blood, coagulation factors, and fluids.

Certain challenging circumstances may demand direct pressure in a unique fashion. Sengstaken-Blakemore tubes have been used to treat penetrating liver injuries with the gastric balloon providing tamponade for retrohepatic bleeding and the esophageal balloon exerting pressure along the liver wound tract.²⁷ Red rubber catheter/Penrose drain/saline-inflated balloon tamponade has also been used successfully for the management of liver injuries.^{28,29} Foley catheter balloon tamponade has been used as an adjunct in selected patients with penetrating neck injuries, allowing stabilization, ancillary testing, and averting surgery for some.³⁰

The most familiar means for achieving definitive hemostasis is the placement of surgical ligatures and clips. These must be placed very accurately so as not to endanger surrounding structures. Small vessels may be managed with simple ligatures while larger arteries should be controlled with a suture ligature to prevent slippage of the tie. In very confined spaces where the placement of ties would be difficult, surgical clips may be applied. Electrocautery produces hemostasis by heating and denaturing proteins, resulting in coagulation. Electrocautery is useful for smaller blood vessels but is insufficient to control large vessel hemorrhage and may result in large areas of tissue necrosis if applied carelessly.

I would be remiss if I did not emphasize the importance of the anesthesia service in the management of these patients. Anesthesia personnel provide the necessary environment, helping to ensure homeostasis, so the surgeon may focus on hemorrhage control in the operating room (and radiology suite). The anesthesiologist also has an important role in controlling bleeding by the transfusion of blood products and maintenance of normothermia.

Topical Hemostatic Agents

Topical hemostatic agents have gained an important place in patient management. The desired properties for the ideal topical hemostatic agent are displayed in Table 3. The mechanisms of action are widely varied; some act by supplying a scaffold for attracting blood elements while others promote coagulation directly (Table 4).³¹

A controlled in vitro analysis of topical hemostatic agents was undertaken by Wagner et al.³² The tested agents included three types of collagen sponges (Actifoam, Davol Inc., Cranston, RI; Helistat,

Integra LifeSciences Corp., Plainsboro, NJ; and Instat, Johnson & Johnson, New Brunswick, NJ), microfibrillar collagen (Avitene, Davol), a gelatin sponge (Gelfoam, Pfizer Inc., New York, NY), and oxidized regenerated cellulose (Surgicel, Johnson & Johnson, New Brunswick, NJ). Actifoam and Avitene caused the greatest response (both statistically similar) in an in vitro platelet aggregation test. Gelfoam exhibited an intermediate response, whereas Helistat, Surgicel, and Instat caused a lesser degree of platelet aggregation. The agents were also tested in their ability to induce gross blood coagulation (Lee-White clotting time). Actifoam, Avitene, and Helistat responded in a manner similar to thrombin, but Instat, Gelfoam, and Surgicel demonstrated no significant impact on clotting time. Wagner and colleagues constructed an overall ranking of these hemostatic agents: Actifoam ~ Avitene > Helistat >> Gelfoam > Instat > Surgicel. It should be noted that this ranking notes differences between the agents for these in vitro assays, and may be limited when considering the varied clinical situations of injured patients.

Fibrin sealant “glue” has been used for lacerations of the liver and spleen. Ochsner et al³³ used fibrin glue as the primary hemostatic agent or as an adjunct to conventional suture repair in 26 patients with hepatic and splenic trauma. Seventeen patients had liver injuries (6 blunt and 11 penetrating) and 9 had splenic injuries (7 blunt and 2 penetrating), all ranging from moderate to severe. Fibrin glue achieved hemostasis in 21 patients with the first application and with the second in the remaining 5 patients. No patients were re-explored for bleeding. Eight patients had postoperative coagulopathy and thrombocytopenia, but the fibrin glue hemostasis remained effective.

FloSeal (Baxter International Inc., Deerfield, IL) is a bovine-derived gelatin matrix mixed with a human-derived thrombin component. After mixture, the agent is spread onto a gauze sponge and placed on the bleeding surface. In a rat liver injury model treated by FloSeal or sham and no additional pressure, mean arterial pressure (MAP) significantly increased in the experimental group, although survival time and mortality were similar to controls.³⁴ In hypothermic swine with grade V renal injuries, FloSeal achieved hemostasis in 60% of animals compared with 0% in controls.³⁵ No delayed bleeding or nephrotoxicity was seen.

Advanced Hemostatic Dressings

Although most topical hemostatic agents are used as adjuncts following control of major hemorrhage, there has been significant interest in the identification of a dressing that can be used for severe uncontrolled bleeding such as that encountered in military applications or the civilian prehospital setting. The ideal advanced hemostatic dressing would quickly and effectively control large vessel hemorrhage under the most adverse conditions with minimal preapplication mixing.^{36,37}

Table 3. Properties of the Ideal Topical Hemostatic Agent

1. Rapid hemostasis of arterial and venous hemorrhage
2. Easily applied and manipulated
3. Holds sutures
4. Little tissue reaction
5. Easily removed
6. Low infectious risk
7. Inexpensive
8. Long storage life

Table 4. Properties of Selected Topical Hemostatic Agents

	Oxidized Cellulose	Collagen	Gelatin	Fibrin "Glue"	Gelatin Matrix/Thrombin
Proprietary name*	Surgicel	Instat Helistat Avitene	Surgifoam Gelfoam	Tisseel	FloSeal
Mechanism	Physical effect; swells after contact with blood aiding in clot formation	On contact with collagen, platelets undergo release reaction, enabling formation of fibrin	On contact with gelatin, platelets undergo release reaction, enabling formation of fibrin. Provides structural support for the forming clot.	Two components must be mixed together for clotting: 1. Fibrinogen + factor XIII 2. Thrombin + CaCl ₂ Fibrinogen is converted to fibrin strands, forming a water-tight matrix that firmly adheres to collagen.	Thrombin converts fibrinogen ultimately to fibrin monomers and fibrin clot. Gelatin particles act to increase adherence.
Time to hemostasis (minutes)	2–8	1–5	Not specified on package inserts	<5	<2
Absorption (weeks)	1–2	8–12	4–6	10–14	6–8
Characteristics	Conforms well; holds sutures	Sponges: conforms and holds suture well. Microfibrillar: packs well, does not hold suture.	Conforms well to surfaces, but does not hold sutures.	Delivered as solution to bleeding surface, forming stable and flexible matrix.	Delivered as solution to bleeding surface. Conforms to irregular surface.
Unique properties	Bactericidal	Holds many times its weight in blood	Holds many times its weight in blood	Can be delivered to deep areas; may be used to seal or glue tissues	Can be delivered to deep areas

*Surgicel, Instat, and Surgifoam, Johnson & Johnson, New Brunswick, NJ; Helistat, Integra LifeSciences, Plainsboro, NJ; Avitene, Davol Inc., Cranston, RI; Gelfoam, Pfizer Inc., New York, NY; and Tisseel and FloSeal, Baxter International Inc., Deerfield, IL.

Fibrin sealant dressings (American Red Cross Fibrin Dressing; Jerome H. Holland Laboratory for the Biomedical Sciences, Rockville, MD) have significantly reduced hemorrhage and improved survival in a swine aortotomy model.^{36,38} The American Red Cross dressing has also been shown to be superior to numerous others by decreasing posttreatment blood loss in a model of swine liver injury.³⁹ A chitosan dressing (HemCon Bandage; HemCon, Inc., Tigard, OR) does achieve initial hemostasis more often than a standard gauze Army field dressing, although failures were seen between 28 and 102 minutes.³⁸ The HemCon bandage is being used under combat conditions by the United States military in Afghanistan and Iraq with promising results.³⁷

QuikClot (Z-Medica Corporation, Wallingford, CT) uses granular zeolite, which promotes clotting by rapidly taking in water molecules from blood while platelets and clotting factors remain, highly concentrated, in the wound. The electrostatic charge (which attracts the water molecules) in each pore of QuikClot is released as heat when the pore is filled. QuikClot is effective in reducing posttreatment blood loss in grade V swine liver injuries, but applicators wore at least two pairs of gloves to tolerate the exothermic reaction (140°F) and hepatic necrosis was found at the liver-QuikClot interface.⁴⁰

Activated Factor VII

Significant work has been done in finding a place for recombinant activated human factor VII (rFVIIa) (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) in the trauma patient. After injury, exposed tissue factor (TF) binds to endogenous factor VIIa, converting factor X to Xa, which in turn produces small amounts of

thrombin from prothrombin. NovoSeven activates factor X directly on the surface of activated platelets at the site of injury, producing large amounts of thrombin. The result is clot formation at the injury site without systemic hypercoagulability.

In the United States, rFVIIa is approved for the treatment of bleeding episodes or prevention of bleeding in surgical interventions/invasive procedures in hemophilia A or B patients with inhibitors to factor VIII or factor IX as well as patients with congenital factor VII deficiency. The first reported use of rFVIIa for trauma was in a wounded 19-year-old soldier with acidosis, coagulopathy, and hypothermia following surgery.⁴¹ After dosing (60 mcg/kg initially followed by 60 mcg/kg 1 hour later), visible bleeding ceased and coagulopathy corrected. Off-label compassionate use of rFVIIa for trauma patients has been increasing as human case series and animal experimentation have shown promise in treating life-threatening bleeding.

When rFVIIa is used as sole therapy for grade IV or V liver injuries in swine, PT is consistently reduced.^{42,43} Other parameters are mixed, however: Schreiber et al⁴² found no changes in MAP or blood loss, while Lynn et al⁴³ found improved MAP but no difference in mortality. Sondeen et al⁴⁴ discovered that rFVIIa increased the MAP at which rebleeding occurred in a porcine aortic hemorrhage model. In coagulopathic hypothermic swine with grade V liver injuries, rFVIIa and packing resulted in a significant decrease in blood loss, and shortened PT.⁴⁵ Animal studies have shown no gross or microscopic thromboembolic events.⁴⁴⁻⁴⁶

Similarly, in numerous massively bleeding patients given rFVIIa after other methods failed to control hemorrhage, a significant reduction in PT has been seen and diffuse bleeding was either markedly reduced or stopped in 5 to 15 minutes.⁴⁷⁻⁵¹ Decreased

requirements for PRBC, FFP, and platelets are also consistently seen after therapy.^{48,51,52} These data have shown no clinical thromboembolic complications.^{47,50-52} Mortality in these patients remains high, however, with rates in excess of 40% to 60% reported.^{47,51,52} Dutton et al⁵¹ found that when coagulopathy recurred after rFVIIa dosing, mortality was 100%.

In the only prospective, randomized, placebo-controlled, double-blind human trial in trauma patients, Boffard et al⁵³ found no difference in composite end points of death, multiple organ failure, and acute respiratory distress syndrome when all patients were considered. In blunt trauma patients, PRBC transfusions were reduced ($P = .02$) as was the need for massive transfusion ($P = .03$).⁵³ In penetrating trauma, there were trends toward reduced PRBC and massive transfusions, but statistical significance was not met. Thromboembolic events were equally divided between treatment and placebo groups.

Futility of rFVIIa therapy may be predicted in certain circumstances of severe injury (Table 5). At pH = 7.0, activity of rFVIIa-TF complex is only 45% of that seen at pH = 7.4, while TF-independent activity is reduced by 90%.⁵⁵ Although TF-dependent rFVIIa activity decreases with hypothermia, TF-independent activity increases in an equal and opposite manner, resulting in a relatively consistent effect over a wide temperature range.⁵⁶ Although not absolute contraindications to therapy, parameters such as these should be considered carefully as part of the context of each patient prior to rFVIIa administration.

Even though rFVIIa has shown promise, patient selection is crucial and optimal dose and timing remain to be elucidated.^{46,47} Patients with injuries clearly incompatible with life should not receive rFVIIa. Current data demonstrate that rFVIIa can be safely used as an adjunct to standard methods of hemorrhage control in injured patients under specific indications (Table 6). Institutions must thoughtfully consider which patients should receive rFVIIa, so that evolving guidelines may help identify patients who are most likely to benefit while minimizing cases of ineffective therapy.

Table 5. Conditions that Compromise rFVIIa Activity

Parameter	Reference
Revised trauma score <4.09	54
Significant coagulopathy (PT ≥17.6)	54
Profound acidosis (pH = 7.0)	54, 55
Hypothermia (decreases TF-dependent activity only)	56

PT, prothrombin time; TF, tissue factor.

Table 6. Proposed Indications for rFVIIa following Injury

Proposed Indication	Reference
Uncontrolled bleeding despite surgical or radiologic control of large-vessel hemorrhage	42, 47, 48
Coagulopathy from exsanguinating hemorrhage and failure of conventional medical hemostatic therapy	42, 47, 51, 54, 55
Significant red blood cell or blood component transfusion requirement	47, 49, 53
Success of transfusion and medical hemostatic therapy unlikely to be timely enough to ensure survival	51
Reasonable hope for meaningful survival if coagulopathy reversed	51-53
Use in remote surgical locations where traditional therapy (platelets, fresh-frozen plasma, cryoprecipitate, rewarming) for traumatic coagulopathy is not available	46

Warfarin

Injured patients taking warfarin require aggressive measures to limit bleeding. Warfarin use predisposes to increased risk of worsened traumatic brain injury and mortality.^{57,58} All patients at risk for brain injury should have an international normalized ratio assay and cranial computed tomography scan.⁵⁹ Ominously, a normal head computed tomographic scan is not predictive of an event-free course as many patients return to the emergency department with a significant intracranial abnormality.⁵⁹

A “Coumadin protocol” ensuring rapid aggressive anticoagulation reversal has been shown to improve mortality.⁶⁰ Thoughtful consideration should be given to the resumption of warfarin therapy if applicable. In a study of patients in whom warfarin therapy was stopped (and not resumed) following trauma, there was no increased risk of stroke or myocardial infarction, although there was a higher risk for venous thromboembolism.⁶¹

Pelvic Fractures

Patients with pelvic fractures require a multidisciplinary approach to hemorrhage control beginning in the emergency department and prehospital setting. Careful physical examination and radiographs are imperative as significant pelvic hemorrhage is seen in 59% to 87% of unstable pelvic fractures but in only 10% to 18% with stable fracture patterns.^{62,63} Bleeding as a result of pelvic fractures is most often due to laceration of venous structures or broken bone edges, and external compression may be effective. A bed sheet securely wrapped across the trochanters is a rapid, noninvasive means to attempt tamponade.^{64,65} Numerous commercial devices and the pneumatic antishock garment (PASG) are also available for this purpose. Circumferential pelvic compression has been shown to reduce externally rotated fractures to a similar extent as definitive stabilization.⁶⁶ Potential hazards of external compression include neurovascular and pelvic visceral injuries as well as pressure ulcers. Krieg et al⁶⁶ found no complications in their series, despite average application duration of 59 hours.

The anterior external pelvic fixator (AEF) may be definitive in stopping venous or cancellous bone bleeding. AEF is most effective in fractures associated with diastasis of the pubic symphysis (“open-book”), as it draws the anterior elements together. An AEF may be applied in the emergency department, operating room, or intensive care unit, usually within 20 to 30 minutes.⁶⁵ The AEF is not effective for fractures involving only posterior elements of the pelvic ring. In these cases, a C-clamp should be used to exert pressure directly across the sacroiliac joint. An experienced orthopaedic surgeon should apply the C-clamp as neurovascular complications may occur.⁶⁵

For patients with bleeding from pelvic fractures in which external fixation is not effective (or not appropriate), bleeding from arteries in the pelvis must be suspected and angiography should be performed. Although relatively uncommon, arterial bleeding is the most frequent cause of death related to pelvic fracture.⁶⁷ Miller et al⁶⁸ found that in patients with hypotension from pelvic fracture, transient or no response to initial resuscitation indicated the presence of arterial bleeding in more than 70%. If an offending artery is identified, embolization may be carried out with either Gelfoam microcoils (Fig. 3) with more than 90% efficacy.⁶⁹ In the absence of other

bleeding sources, repeat angiography should be performed if there is persistent hypotension, high transfusion rate, or more than two arteries bleeding at first embolization.⁷⁰ New bleeding sites are seen in 68%, bleeding at previously embolized sites in 18%, and both in 14%.⁷⁰

Angiography for Lesions Outside the Pelvis

Angiography with embolization clearly complements surgical damage control in a wide variety of circumstances.^{71,72} This modality has been shown to be effective (>90% efficacy) for liver, spleen, and renal injuries.^{69,73,74} Adding a “splenic protocol” in one trauma program led to fewer laparotomies and improved splenic salvage with similar mortality and complication rates compared with earlier approaches used by the authors (Fig. 4).⁷⁵ Algorithms such as this can be adapted to meet the specific needs of individual institutions. Successful embolization of extrathoracic chest wall bleeding has been reported.⁷⁶

Pneumatic Antishock Garment

The PASG is used to control bleeding in patients with pelvic and lower extremity fractures by acting as a splint to exert tamponade. It can be used for hypovolemic shock (without fracture), but it is only a temporizing measure. In healthy volunteers, PASG use resulted in unchanged cardiac output and carotid/subclavian blood flow, but inferior to the edge of the trousers, blood flow approached zero.⁷⁷ Therefore, prolonged use may be associated with numerous complications, such as compartment syndrome.



Figure 3. Microcoils used in pelvic arterial embolization. (Photograph courtesy of James Newman, MD, PhD.)

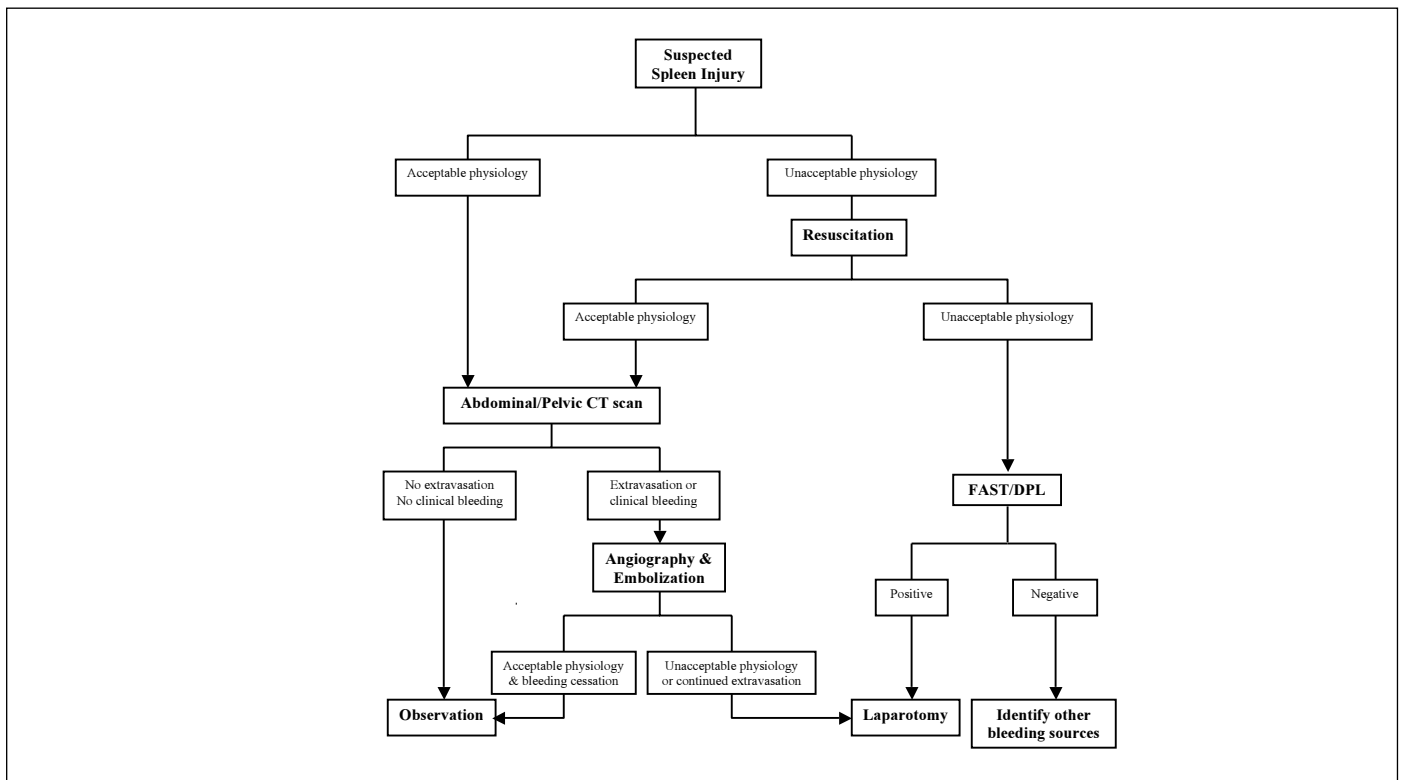


Figure 4. Spleen injury treatment algorithm using angiography and embolization. CT, computed tomography; DPL, diagnostic peritoneal lavage. (Modified from Gaarder C, Dormagen JB, Eken T, et al. Nonoperative management of splenic injuries: improved results with angioembolization. *J Trauma* 2006;61(1):192-8.)

In hypotensive pigs, Ali and Qi⁷⁸ found that PASG use resulted in significant increases in serum potassium and lactate, tissue edema, and fluid requirements. Myonecrosis has been found in uninjured extremities with PASG use in trauma patients.⁷⁹

PASG should be used as a temporizing measure with the shortest inflation time possible and probably should not be used if time to definitive care is short. Of surveyed trauma practitioners, 52% recommended use of PASG if transport time was 20 to 40 minutes, but only 24% supported use if transport time was less than 15 minutes.⁸⁰ Cayten et al⁸¹ identified a possible survival advantage in severely hypotensive patients, although Chang et al⁸² have found no such benefit.

Tourniquets

Tourniquet use is controversial. They may be life-saving, but there are very real hazards associated with their use or misuse. Using a tourniquet when not indicated could lead to amputation of a salvageable limb. Not using a tourniquet when indicated could result in death. Poor application may actually increase bleeding by impeding venous outflow, while failing to occlude the offending artery.⁸³

Even in trained hands, tourniquet use is not always a clear-cut matter. In a 4-year analysis of tourniquet use by Israel Defense Forces soldiers, although overall effectiveness was 97% and no deaths resulted from uncontrolled hemorrhage, 47% of applications were deemed “not indicated.”⁸⁴ Tourniquets should be used only when bleeding is life-threatening, conventional measures have failed, the consequences of application can be managed, scene safety issues are significant, and a lack of resources exists to maintain direct pressure.^{85,86} Although there is no perfect tourniquet design, qualities demanded by the United States military include (1) stopping blood flow reliably, (2) light weight, (3) compact size, (4) quickly and easily applied (with one hand, if possible), and (5) for use on both upper and lower extremities.⁸⁷

Safe principles for care of the patient with a tourniquet should include (1) used for the shortest time possible and removed at the first available opportunity, (2) should be deflated for 10 minutes every 2 hours, (3) use wide cuffs to allow for lower occlusion pressure, (4) record the time when applied, (5) communicate tourniquet use to others “down the line” in the care process, and (6) should be removed by medical personnel only if bleeding can be managed and resuscitation carried out.^{86,88,89}

Summary

Hemorrhage control is a multidisciplinary endeavor. Lacerated organs and blood vessels must be resected or repaired before the sequelae of hemorrhage ensue. Medical therapy using blood products, rFVIIa, topical hemostatic agents, or advanced hemostatic dressings may also be required to help restore, or compensate for, a depleted coagulation system. Numerous methods for hemorrhage control exist, but each modality must be applied to the appropriate situation. Communication between the surgeon and anesthesiologist must be of the highest quality, so that appropriate corrective actions may be undertaken to preserve life.

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Hemostatic Drugs in Trauma and Orthopaedic Practice

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Learning Objectives: 1) To define the pharmacologic interventions that can be administered to humans to help reduce bleeding and the need for transfusions in patients having elective orthopaedic surgery or who have suffered trauma. 2) To describe that the data suggest that lysine analogue antifibrinolytics have shown more efficacy in simple joint arthroplasty, but there is more evidence for efficacy of aprotinin in major joint surgery. 3) To describe the lack of high-level studies in acute trauma to show efficacy of hemostatic drugs in reducing bleeding. 4) To consider potential safety issues related to the use of these compounds in trauma and orthopaedic surgery

Abstract

Surgery carries a high risk for bleeding. Hemostatic drugs are one method of blood management. This review highlights hemostatic drugs that enhance and stabilize clots and aim to decrease the hemorrhage and blood transfusion rates in elective and emergency situations in orthopaedic surgery and trauma situations. The current evidence for benefit of these drugs and their risks are discussed. They need to be used appropriately as part of our blood management armamentarium.

Orthopaedic surgery and trauma that result in major blood loss increase morbidity and mortality. In trauma, uncontrolled hemorrhage is the leading cause of preventable death.¹ In elective orthopaedic surgery, blood loss produces transfusion rates that vary from 11% to 65%, depending on the type of surgery.²

Blood transfusion may be a life-saving measure in hemorrhage but is an expensive resource that can result in a variety of problems for our patients. Allogeneic transfusion carries the risk of infection transmission, immune suppression, anaphylaxis, volume overload, transfusion-related lung injury, and graft-versus-host disease. Transfusion of packed red cells can also cause hypothermia and coagulation factor deficiencies, which can lead to a coagulopathy, which may cause continued bleeding. Finally, transfusion may also

be refused by patients because of religious or personal beliefs, even in emergency situations.

This review focuses on drugs that enhance and stabilize clots and aim to decrease the hemorrhage and blood transfusion rates in the elective and emergency situation in orthopaedics and trauma.

Hemostatic Drug Types

The various drugs that have some efficacy in humans having a variety of surgeries is shown in Table 1

Aprotinin is a nonspecific, naturally occurring serine protease inhibitor, derived from bovine lung. Its mechanism is complex and multifactorial.³⁻⁵

Aprotinin stabilizes blood clots by decreasing plasmin-mediated fibrinolysis. It does this directly by inhibiting plasmin and indirectly by inhibiting urokinase (which activates plasminogen to plasmin) and kallikrein (which has the dual effect of increasing plasmin and increasing activation of the intrinsic pathway of coagulation). The inhibition of the latter action of kallikrein may be important in limiting excessive coagulation, which would lead to a hypercoagulable state. Aprotinin also has platelet-stabilizing properties by stabilization of platelet glycoprotein function associated with adhesion and aggregation.

Also, aprotinin is approved by the Food and Drug Administration for patients having coronary artery bypass graft surgery who are at increased risk for blood loss and transfusion. It has also been used successfully for hemostasis in orthopaedic, transplantation, colorectal, and peripheral vascular surgery.^{5,6}

Nafamostat is a synthetic protease inhibitor that inhibits thrombin, factors Xa and XIIa, kallikrein, plasmin, and complement factors (C1r, C1s). Similar in nature to aprotinin, it works as an antifibrinolytic, anticoagulant, and anti-inflammatory agent, and has been shown to preserve platelet function during cardiopulmonary bypass. Several Japanese studies⁷⁻⁹ show a significant reduction in postoperative blood loss in cardiac surgery with its use. Nafamostat has been studied in relation to cardiac surgery in Italy and Norway but it has not yet been used in human studies in the United Kingdom or the United States for the purpose of blood loss reduction, and it has not yet been used in orthopaedic surgery

ϵ -Aminocaproic acid and its analogue, *tranexamic acid*, are derivatives of the amino acid lysine. Both of these drugs inhibit the conversion of plasminogen to plasmin by preventing the binding of plasminogen to fibrin(ogen). Plasmin breaks down fibrinogen and a series of other proteins involved in coagulation. Tranexamic acid is 6 to 10 times more potent than ϵ -aminocaproic acid and has a longer half-life. Tranexamic acid has also been found to penetrate into joints well, with a drug concentration in joint fluid comparable to that in serum.¹⁰

Table 1. Various Drugs Agents That Have Some Efficacy to Reduce Bleeding and/or Transfusion Burden

Generic Name	Pharmacologic Class
Aprotinin	Natural serine protease inhibitor
Nafamostat mesylate	Synthetic serine protease inhibitor
ϵ -Aminocaproic acid	Lysine analogue
Tranexamic acid	Lysine analogue
Desmopressin	Analogue of arginine vasopressin
Recombinant activated factor VII	Clotting factor and thrombin generator