

# 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.<sup>1</sup> In elective orthopaedic surgery, blood loss produces transfusion rates that vary from 11% to 65%, depending on the type of surgery.<sup>2</sup>

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.<sup>3-5</sup>

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.<sup>5,6</sup>

*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 studies<sup>7-9</sup> 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

$\epsilon$ -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  $\epsilon$ -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.<sup>10</sup>

**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
$\epsilon$ -Aminocaproic acid	Lysine analogue
Tranexamic acid	Lysine analogue
Desmopressin	Analogue of arginine vasopressin
Recombinant activated factor VII	Clotting factor and thrombin generator

*Desmopressin*, an analogue of arginine vasopressin, stimulates the endothelial release of factor VIII and von Willebrand factor via the V2 receptor.<sup>11</sup> These factors increase platelet aggregation. Desmopressin is used in patients with mild hemophilia A or type 1 von Willebrand disease and in patients with uremia-related platelet abnormality. There are also data supporting its use to reduce blood loss in patients taking aspirin in cardiac surgery.<sup>12</sup> However, in patients undergoing orthopaedic surgery, there is no proven benefit in patients without pre-existing hematologic diseases.<sup>13</sup>

*Recombinant factor VIIa* (rFVIIa) acts by formation of tissue factor-factor VIIa complex at the site of endothelial damage and thereby enhances the natural coagulation pathway. This makes the rFVIIa effect highly localized. In supraphysiologic doses it can also bind to activated platelet membranes where it activates factor X directly, which leads to a massive rise in thrombin generation at the platelet surface. rFVIIa has not been approved for use in surgery and trauma. From a practical perspective, its cost limits its use to life-saving trauma situations and surgery with excessive bleeding in which all other measures have failed.

## Elective Orthopaedic Surgery

### Primary Knee or Hip Arthroplasty

In a recent meta-analysis,<sup>14</sup> aprotinin use showed a statistically significant reduction in allogeneic blood transfusion compared with placebo, whatever the type of orthopaedic procedure. Rates of transfusion in patients having a variety of major orthopaedic surgeries fell from 44.4% in those patients allocated to the placebo arm of the studies to 22%. The odds ratio (that is, the ratio of the risk of the event for the aprotinin versus the placebo group) for transfusion was calculated as 0.42 (95% confidence interval [CI]: 0.22-0.66). The total perioperative blood loss was also significantly decreased with aprotinin after primary hip or knee surgery. The odds ratio was 0.41 (95% CI: 0.22-0.74). The level of evidence for aprotinin use was much stronger in hip surgery<sup>15,16</sup> than knee surgery, with only two small studies reported.<sup>14</sup>

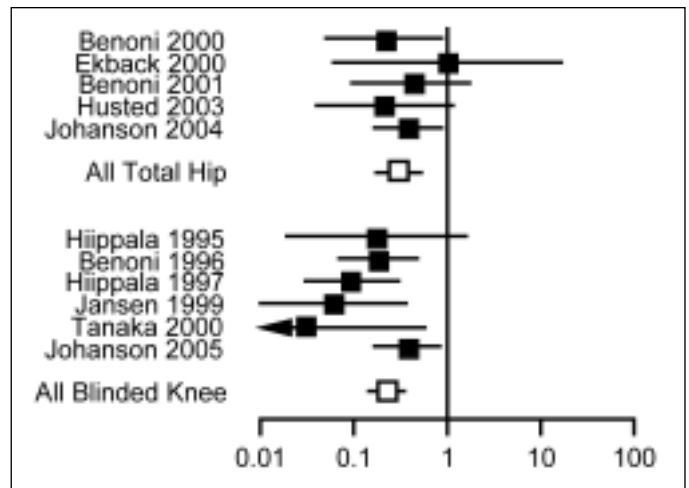
Interestingly, the dose regimen used did not appear to significantly alter these results. This is very different finding to the pattern seen in cardiac surgery<sup>3</sup> or hepatic transplantation,<sup>17</sup> in which it is more clearly seen that higher doses have a more pronounced reduction in transfusion rates.

Orthopaedic trials with tranexamic acid performed in primary hip or knee arthroplasty show greater efficacy in allogeneic transfusion reduction in knee arthroplasty using an exsanguinating tourniquet. In six double-blind studies, the rate of transfusion fell from 74.7% to 40% (odds ratio, 0.11 [0.06-0.18] when compared with placebo). For hip arthroplasty the data from five studies showed a reduction in transfusions from 38.9% to 16.6% (odds ratio, 0.29 [0.17-0.52] compared with placebo). The data for odds ratios for the individual studies and in combination are shown in Figure 1.

Tranexamic acid appears to be more efficacious when a dose of more than 30 mg/kg is used and also when a repeated bolus or single bolus followed by infusion is used instead of single bolus.<sup>14</sup> The most common regimen in the studies involves two intravenous boluses (10–15 mg/kg), the first one given before skin incision or deflation of the tourniquet and the second 3 hours later.  $\epsilon$ -Aminocaproic acid use did not show any significant reduction in blood loss or reduction in transfusion.<sup>14</sup>

### Complex Elective Orthopaedic Surgery

As already seen in cardiac surgery,<sup>18</sup> the greater the degree of bleeding the more apparent the beneficial effects of aprotinin appear



**Figure 1.** Depiction of odds ratios for transfusions in the individual studies (closed squares are ratio and lines represent 95% confidence intervals) of those patients having total hip arthroplasty and those patients taking part in blinded, randomized studies of knee arthroplasty. All studies shown in this figure compared tranexamic acid with no drug. Although overall meta-analyses (shown as open squares) suggest significant efficacy in both operations, it is clear that only one of the individual studies in hip surgery showed efficacy, whereas only one of the blinded studies in knee surgery performed using an exsanguinating tourniquet failed to show efficacy.

to be. There is a stronger case for using aprotinin in situations where there is a higher risk of blood loss; for example, revision, bilateral, or spinal surgery, and surgery for cancer or sepsis.

A randomized controlled trial (RCT) by Murkin et al<sup>16</sup> investigated the use of aprotinin versus placebo in revision total arthroplasty or bilateral total hip arthroplasty. In the aprotinin group, there were significantly decreased average total blood loss and transfusion requirements. Average total blood loss decreased from 2096 to 1,498 mL ( $P < .022$ ) and average transfusion requirements decreased from 2.9 to 2.0 units (average difference, 0.9 unit with 95% CI: -1.69 to -0.07).

Another RCT by Jeserschek et al<sup>19</sup> found reduced blood loss with aprotinin in revision hip or knee or sarcoma surgery. They also found a decrease in mean hospital length of stay from 27.8 days in the control group to 17.6 days in the aprotinin group.

Two RCTs in adults<sup>20,21</sup> and another in children<sup>22</sup> using different dose regimens showed that in spinal surgery, aprotinin made significant reductions in both blood loss and transfusion requirements. However, a further RCT in pediatric scoliosis surgery, showed reductions in blood loss and transfusion that were not significant statistically.<sup>23</sup>

In patients with malignancy, Amar et al.<sup>24</sup> found no significant difference with aprotinin in either blood loss or transfusion requirements. Capdevila et al.,<sup>25</sup> however, showed that in patients with malignancy or sepsis, aprotinin showed a major reduction in blood loss (1,783 versus 5,305 mL in the placebo group) and packed red cell units (3 versus 7).<sup>19</sup> This difference may be because of the lower risk of bleeding of patients in the trial by Amar et al, as average blood loss in the placebo group was 1,300 mL.

This difference between study reports led to a randomized, double-blind study of aprotinin in major orthopaedic surgery, including revision spine or hip surgery, trauma surgery, cancer surgery, or surgery for sepsis with an expected blood loss of more than 2,000 mL. This study showed a significant and dramatic reduction in measured and calculated bleeding and the amount of

transfused blood with large-dose aprotinin (4 M kallikrein inhibitory units [KIU] plus 1 M KIU/h).<sup>26</sup> Total transfusions of allogeneic blood fell from 101 units administered to the 18 patients allocated to the placebo arm of the study to 7 units only to the 18 patients in the higher-dose aprotinin arm.

This dose is much larger than the “high” or “full” doses used in other trials, and it was proposed that the lesser or variable results with other doses may be the result of significant bleeding causing partial washout of the drug. The full dose when used in cardiac surgery may be beneficial because of blood being reinfused through the bypass circuit or extra doses being given by the perfusionists.

Tranexamic acid has not yet been formally tried in more complex joint surgery, but a trial in Texas is now being carried out with tranexamic acid in revision hip arthroplasty.

One study for pediatric scoliosis surgery using tranexamic acid, cell salvage, and permissive anemia (transfusion trigger, 7.0 g/dL) showed significantly reduced blood transfusion but no change in apparent blood loss,<sup>27</sup> whereas a more recent study showed significantly reduced blood loss but not reduced transfusion rates.<sup>28</sup>

Prophylactic use of rFVIIa was investigated in a double-blind RCT by Raobaikady et al<sup>29</sup> in patients undergoing open reduction of traumatic pelvic and pelvic acetabular fractures (historically, these patients have a mean blood loss of about 2.5 L). The measured blood loss in the rFVIIa group was greater than that in the placebo group (2,070 vs. 1,535 mL). There was a trend toward less total blood loss at 48 hours and less allogeneic blood components, but these latter findings were not significant statistically. The authors concluded that prophylactic rFVIIa use was not justified in patients with normal clotting systems.

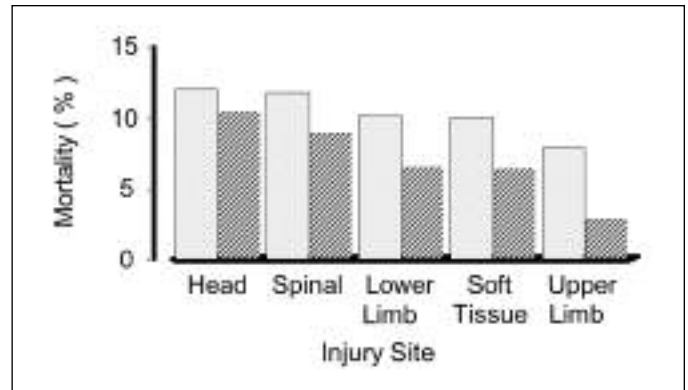
## Trauma

In one early multicenter study from Germany<sup>30</sup> in 1976, involving 4,686 patients, the effects of aprotinin in traumatic shock were studied. The dose used was approximately 3 million KIU during 2 days; this relatively low dose produced a significant decrease in mortality when administered within a few hours of trauma. The most significant outcome benefits with aprotinin were found in patients with injuries to upper extremity and soft tissues, but there were also significant benefits after trauma to the lower limb and spine. The data for the relative mortalities in each of the groups are shown in Figure 2.

A Cochrane systematic review of RCTs using aprotinin, tranexamic acid, or ε-aminocaproic acid in trauma concluded that there was only one useful study in the literature.<sup>31</sup> Even this study was small, with very imprecise estimates for outcomes, and data on the proportion requiring blood transfusion were not reported. It was concluded that there was insufficient RCT evidence to reach an opinion regarding their potential benefit.

CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage) is a large international multicentered, placebo-controlled RCT currently underway. The study aims to recruit 20,000 patients to assess the value of tranexamic acid in trauma. Tranexamic acid has been chosen because of the cost of aprotinin.

Military use of rFVIIa in Iraq has shown a mortality benefit<sup>32</sup> but this was a retrospective study and was not randomized. A recent review of rFVIIa use showed that it was usually used as salvage therapy when other appropriate hemostatic methods had failed.<sup>33</sup> The doses varied widely between 36 and 178 mcg/kg, with patients receiving a single dose or multiple doses at 2- to 12-hour intervals. Efficacy of treatment (reduction in blood loss, transfusion



**Figure 2. Percentage mortality in groups of patients with trauma and tissue injury with (hatched bars) and without (clear bars) aprotinin therapy. Data are drawn from tabulated data in Schneider et al<sup>30</sup> and are from a total of more than 4,000 patients. Mortality rates are significantly lower in aprotinin-treated patients for upper limb and soft tissue injury ( $P < .01$ ) and also for lower limb trauma and spinal injury ( $P < .05$ ). There was no significant difference between treatment or no treatment in patients with predominantly head injuries.**

requirements, and mortality) was reported for 79.4% of patients. Most publications also described normalizing of coagulation parameters after administration.

The European guideline on the management of bleeding following major trauma<sup>34</sup> does recommend the appropriate use of hemostatic drugs, including tranexamic acid, ε-caproic acid, aprotinin, and in situations in which other measures have been unsuccessful rFVIIa.

## Risks

The main theoretical risk of hemostatic drugs is excess coagulation forming thrombosis in the venous or arterial system. The meta-analysis by Zufferey et al<sup>14</sup> did not show a statistically significant increase in risk of venous thromboembolism with the either aprotinin, tranexamic acid, or ε-aminocaproic acid. Haas<sup>35</sup> also found no association between aprotinin use and the prevalence of deep vein thrombosis.

Aprotinin may result in anaphylaxis in some patients. The incidence of hypersensitivity is higher (5%) if re-exposure occurs within 6 months of previous aprotinin administration, and decreases again (to 0.9%) for re-exposure after 6 months.<sup>36,37</sup> A 1-mL test dose intravenously, and then waiting for at least 10 minutes before the loading dose, is recommended.

The Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation reported an international multicentered prospective observational study of 4,374 patients that suggested that aprotinin given during coronary artery bypass surgery increased the risk of renal impairment, myocardial infarction, or heart failure, and stroke.<sup>38</sup> The same group has also followed these patients and found that the 5-year mortality in the aprotinin group was significantly higher than in controls.<sup>39</sup> Both of these studies have found no end-organ failure or increase in mortality for tranexamic acid and aminocaproic acid.

These two studies are controversial, as a Food and Drug Administration advisory committee that met in September 2006 had queries concerning the methodology of the former, and also queried apparent differences between this and previously published articles from the same dataset.<sup>40</sup> The latter trial did not publish the causes of

death. Moreover, the choice of drug intervention was not randomized and there were significantly more higher-risk patients allocated by their health care team to receive aprotinin.<sup>41</sup>

Tranexamic acid has been found to produce gastrointestinal effects when given orally, but this has not been reported with intravenous administration. Rapid intravenous boluses may cause hypotension, so it is recommended that it is given either over 10 minutes or via an infusion.<sup>13</sup> Although its dose needs to be reduced in cases of renal impairment as it is mostly excreted unchanged by the kidneys, there is little evidence to suggest renal toxicity apart from one study<sup>42</sup> that reported that an infusion that continued for 12 hours postsurgery showed a tendency to increased renal dysfunction.

$\epsilon$ -Aminocaproic acid also produces hypotension with rapid intravenous administration. It is teratogenic and therefore is contraindicated in pregnancy.<sup>13</sup>

Desmopressin administration is associated with mild facial flushing and headache. More worrisome hypotension occurs in about 40% of patients. It may also cause adverse effects because of its antidiuretic action (water retention and hyponatremia)

An analysis of almost 2,000 patients treated with rFVIIa showed no venous or arterial thrombotic events.<sup>43</sup> However, a total of 185 thromboembolic events in 168 patients who received rFVIIa during a 5-year period have been the subject of spontaneous adverse events reporting to the U.S. Food and Drug Administration.<sup>44</sup>

## Discussion

With surgery that is known to be high risk for bleeding, we continue to search for methods to improve our results. Hemostatic drugs are one part of our blood-management armamentarium.<sup>45-48</sup> Reducing the risk of bleeding starts preoperatively with risk assessment, optimization of anemia, and consideration of erythropoietin and preoperative autologous blood donation. Intraoperatively, surgeons may modify outcome by adapting surgical technique, use of hemostatic devices (e.g., tourniquet), patient positioning, and locally applied hemostatic agents (e.g., fibrin glue) and eliminating drains. Anesthesiologists may use acute normovolemic hemodilution, hypotensive anesthesia, cell salvage, and also hemostatic drugs.

Postoperatively, transfusion triggers should be individualized to avoid overcorrection. Cell salvage and hemostatic drugs may also be used at this stage.

Hemostatic drugs therefore need to be used appropriately in conjunction with these other methods as the causes of orthopaedic and trauma blood loss and transfusion are multifactorial, and different causes may be prevented or have their effects modified differently. Hemostatic drugs are used not only systemically by anesthesiologists but have been used topically in combination with fibrin sealants by orthopaedic surgeons.<sup>49</sup>

Hemostatic drugs are useful in excessive generalized bleeding due to hyperfibrinolysis, mild hemostatic defects, or in those patients refusing blood products.<sup>13</sup> The appropriate drug is most effective when given as prophylaxis and when adequate doses are given so that they are not lost with the hemorrhage. Localized bleeding is usually most appropriately managed surgically or radiologically, but may require hemostatic drugs if continued blood loss and replacement causes secondary coagulopathy.

Aprotinin has the best evidence to support its efficacy in cardiac surgery, but in major orthopaedic surgery the evidence to support its use or that of the lysine analogues, which are cheaper, is much less strong. rFVIIa is a newer drug that is most often used as salvage therapy in trauma and uncontrolled hemorrhage in major surgery

when other measures have failed. Its use is limited by its high cost.

Results of ongoing trials of hemostatic drugs in orthopaedic surgery and trauma are awaited to better determine their optimal uses, doses, timing of administration, and safety.

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