ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Antifibrinolytic Agents in Acquired Bleeding Disorders

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H&O What are the main causes of acquired coagulopathy?

MW We categorize these based on what can go wrong along the many pathways of coagulation: decreased coagulation factor synthesis; increased clearance of coagulation factors caused by consumption, hemodilution, or an immune effect; or inhibition of coagulation factor enzymatic activity. Possible causes include liver disease; medication that inhibits vitamin K; the use of novel oral anticoagulants, factor Xa inhibitors, direct thrombin inhibitors, or antiplatelet agents; uremia; or disseminated intravascular coagulopathy. Other possible causes are acquired von Willebrand disease, which is uncommon, and acquired hemophilia, which is rare. One of the most important acquired causes of bleeding is trauma-induced coagulopathy, which can result from many factors and has a very high mortality when accompanied by fibrinolysis.

H&O What agents are used to prevent and treat bleeding in acquired coagulopathy?

MW We use tranexamic acid (TXA) to prevent bleeding in patients undergoing elective orthopedic surgery, including major surgery of the hip or knee. TXA given either systemically or locally has been shown to reduce the need for blood products dramatically. TXA is not currently used in emergency orthopedic surgery, however.

For the treatment of patients with acquired coagulopathy who are bleeding or require surgery, we usually use blood products such as platelets, fresh frozen plasma (FFP), and cryoprecipitate in addition to packed red blood cells when indicated. In Europe, soluble fibrinogen concentrate and prothrombin complex concentrate (PCC) are used. Depending on the underlying cause, we may also administer vitamin K, FFP, or PCC to replenish factors II, VII, IX, and X. We turn to cryoprecipitate or soluble fibrinogen concentrate where available for the treatment of hypofibrinogenemia. We provide concentrates of specific factors to treat acquired deficiencies caused by acquired inhibitors of factors. We recently adopted early use of the lysine analogues—aminocaproic acid or TXA—to treat trauma-induced coagulopathy. We use desmopressin acetate (DDAVP) when necessary to increase factor VIII and von Willebrand factor (VWF). We occasionally use VWF replacement concentrate and platelets in surgery and in major bleeding events that are associated with acquired VWF deficiency that fails to respond to DDAVP. We turn to the reversal agent protamine for bleeding related to unfractionated heparin and low-molecular-weight heparin.

Bleeding associated with the novel oral anticoagulants is treated with a specific reversal agent for the direct thrombin inhibitor dabigatran. For the other direct thrombin inhibitors and anti–Xa inhibitors, we provide empiric treatment with PCC with or without recombinant factor VIIa (rFVIIa), or factor VIII inhibitor bypassing activity (FEIBA), depending on the anatomic locality and severity of bleeding, and occasionally we add TXA. For bleeding associated with pentasaccharides, thrombolytic agents, and antiplatelet agents, varying approaches exist regarding the use of FFP, cryoprecipitate, soluble fibrinogen concentrate, PCC, FEIBA, rFVIIa, platelets, DDAVP, and antifibrinolytic agents, depending on the anatomic locality and severity of bleeding.

H&O Could you talk more about the lysine analogues TXA and aminocaproic acid?

MW In the presence of TXA, the lysine receptor binding sites of plasmin for fibrin are occupied, preventing binding to fibrin monomers, thus maintaining fibrin's structure and preventing its breakdown.

H&O How do physicians determine when to use these agents?

MW The answer to that is somewhat controversial in acute trauma, when clinical decisions must be made quickly in certain instances. As I mentioned earlier, we use TXA in most patients who are undergoing elective hip or knee surgery. We can also use TXA in women with menorrhagia. Another use is for epistaxis, in which we insert a tampon saturated with TXA and a local vasoconstrictor such as metolazone into the nose. TXA also has been used to treat dental bleeding and hyphema, which is bleeding in the anterior chamber of the eye. Studies are looking at the use of TXA to treat postpartum bleeding (WOMAN; World Maternal Antifibrinolytic Trial; NCT00872469) and gastrointestinal bleeding (HALT-IT; Haemorrhage Alleviation With Tranexamic Acid-Intestinal System; NCT01658124). Finally, the CRASH-3 trial is underway that is evaluating the efficacy of TXA to reduce bleeding in traumatic brain injury (NCT01402882).

TXA also can be given empirically to treat patients with bleeding from trauma, as shown in the CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage), which was published in the *Lancet* in 2010. We in the United States and many other centers worldwide limit the initial dose to patients who are in shock from trauma; we then use point-of-care testing—thromboelastography (TEG) or rotational thromboelastometry (ROTEM)—to determine the need for a subsequent dose of TXA. Many other centers give TXA to all patients with hemorrhage and trauma whether they are in shock or not. The indications for the use of TXA in trauma remain a matter of significant debate.

TXA must be given within the first 3 hours after trauma, which means we need to rapidly obtain reliable information about the state of fibrinolysis. It takes too long for the standard coagulation tests that we use—prothrombin time, activated partial thromboplasmin time, platelet counts, fibrinogen levels, fibrin split products, and D-dimers—to produce results, and they do not provide a good idea of whether a patient has clinically significant fibrinolysis.

Attempts have been made to define fibrinolysis with levels of plasmin-antiplasmin complex, which is very sensitive, but it is unknown whether these tests will prove to be useful on a widespread clinical basis.

Another problem from a research standpoint is that the TEG and ROTEM cutoff values for fibrinolysis are not standardized and vary from institution to institution. Work is currently being done to further define latent fibrinolysis with the so-called tPA challenge test, in which increasing doses of tPA are added to a sample to determine the presence or absence of underlying fibrinolysis.

H&O What are the advantages of lysine analogues over other products to arrest bleeding, such as fresh frozen plasma?

MW They are inexpensive, easy to store and administer, and effective when fibrinolysis is present. TXA has been shown in many randomized controlled trials to prevent bleeding in heart surgery, liver transplant, and elective orthopedic surgery, and it is reasonable to assume that the same occurs in patients who have trauma. The administration of TXA may allow us to reverse bleeding more quickly and use less blood component in patients with severe shock. Many ongoing randomized controlled trials are looking at this concept in trauma.

H&O What are the side effects of lysine analogues?

MW They have been shown to be very safe, although patients who receive them may also receive a high volume of fluid, which can be harmful in cases of trauma. There is also an unknown incidence of thrombosis following the use of lysine analogues, which is an interesting area of research. Results from CRASH-2 showed no increased incidence of thrombosis, although the authors of the study suggested in the paper that they may have underestimated the incidence of thrombosis. We await confirmation of this finding in further randomized controlled trials.

Nonrandomized controlled trials after CRASH-2 have shown an increased incidence of venous thromboembolism (VTE) with lysine analogues. This is very interesting given that a hypercoagulable state can manifest hours, days, or even weeks after trauma. Patients in whom this hypercoagulable state, called fibrinolytic shutdown, develops have an elevated risk for mortality due to increased obstruction of the microvasculature. Could TXA be causing this? This question is entirely theoretical but of interest.

The other side effect we see with lysine analogues is an increase in seizures and strokes. This complication was noted in the recently published ATACAS trial (Aspirin and Tranexamic Acid for Coronary Artery Surgery) by Myles and colleagues. This study, which looked at the use of TXA to prevent blood loss during cardiac surgery, demonstrated that TXA significantly reduced bleeding. The increases in seizures and strokes were attributed to increased local cerebral thrombotic complications caused by TXA.

Table. Studies That Have Evaluated the Risk for Venous Thromboembolism Related to Tranexamic Acid in Patients With Trauma[a]

Study	Entry Criteria	N			Mean ISS			Rate of VTE		
		Total	TXA	No TXA	TXA	No TXA	*P* Value	TXA, %	No TXA, %	*P* Value
Randomized controlled trials										
Shakur et al, 2010	Adult trauma patients with, or at risk for, significant bleeding	20,127	10,060	10,067	NA	NA	NA	1.7[b]	2.0[b]	0.084
Yutthakasemsunt et al, 2013	Adult trauma patients with moderate to severe traumatic brain injury (post-resuscitation Glasgow Coma Scale score of 4 to 12)	238	120	118	NA	NA	NA	0	0	–
Observational studies										
Morrison et al, 2012	Patients who received at least 1 unit of PRBCs within 24 h of admission following combat-related injury	896	293	603	25.2	22.5	<0.001	2.7	0.3	0.001
Swendsen et al, 2013	Adult trauma patients who met triage criteria for serious injury and had at least one of the following: hypotension, massive transfusion guideline activation, or transport directly to the operating room or interventional radiology suite	126	52	74	27.1	20.5	0.02	11.5	0	0.004
Van Haren et al, 2014	Adult trauma patients with hypercoagulable state defined as Greenfield RAP ≥10	121	27	94	31	26	0.117	33	27	0.492
Harvin et al, 2015	Adult trauma patients with hyperfibrinolysis determined by rapid thromboelastography	1032	98	934	29	14	<0.001	6.3	4.4	0.389
Cole et al, 2015	Adult trauma patients with severe injury defined as ISS >15	385	160	225	33	29	<0.05	5	4	NS
Wafaisade et al, 2016	Trauma patients with/without prehospital TXA administration	516	258	258	24	24	0.46	5.6	8.3	0.58

ISS, injury severity score; N, number of patients; NA, not available; PRBC, packed red blood cell; RAP, risk assessment profile; TXA, tranexamic acid; VTE, venous thromboembolism.

[a] These data represent 20,365 patients from 2 randomized controlled trials and 2752 patients from 6 observational studies. The pooled relative risk for VTE was 0.84 (95% CI, 0.68-1.02) in the randomized controlled trials and 1.61 (95% CI, 0.86-3.01) in the observational studies.

[b] These data indicate the rate of pulmonary embolism.

H&O Could you describe CRASH-2 and your own take on it?

MW CRASH-2 was a large, double-blinded, randomized controlled trial in which more than 20,000 adult patients with trauma who had or were at risk for significant bleeding were randomly assigned to either TXA or placebo. This was a benchmark study of the use of the antifibrinolytic procoagulant TXA to treat trauma-induced coagulopathy. The study clearly found a statistically significant reduction in mortality with TXA.

Several interesting points were raised by this study, however. First, many of the patients included did not necessarily require antifibrinolytic treatment. Recruitment to this trial was determined by the uncertainty principle, meaning that enrollment was limited to patients whose physicians were unsure whether to administer antifibrinolytics. Physicians did not administer TXA to patients who clearly did not need it and did not withhold the agent from those who clearly did need it in order to ensure that the trial was ethical. This principle is called equipoise. Patients were then randomly assigned to treatment with either TXA or matching placebo. As Cap and colleagues wrote about the CRASH-2 trial, "[a]lthough this design may seem to introduce excessive physician discretion in determining patient eligibility, it should be clear that clinical equipoise could be the only ethical basis for enrolling patients in the study."

Second, CRASH-2 found no reduction in the number of blood transfusions among the patients who received TXA. That raises the question of how TXA works. For example, it is possible that it may work in trauma by reducing inflammation.

Third, even though this study involved 20,211 patients in 274 hospitals across 40 countries—many of them developing countries where one of the criteria for trial inclusion was for the hospital to have a phone—the 28-day follow-up rate was nearly 100%. That is an incredible achievement and has been commented on by many authors, including a group of trauma specialists on behalf of the Department of Defense. Other problems were the small sample sizes of patients with hypotension (31.5%) or tachycardia (48%), who were the target populations; and that the main cause of death was traumatic brain injury rather than bleeding.

Finally, as the authors themselves admit in the study, they may have underestimated the incidence of VTE in CRASH-2.

Because of the results of this study, TXA is now being given to many trauma patients in the United Kingdom. In fact, local emergency services in the United Kingdom are not reimbursed by the National Health Service if roadside TXA is not administered when "necessary and appropriate." The "necessary and appropriate" indications for prehospital TXA administration are still a matter of conjecture in both Europe and the United States. We have been slower to use it in the United States because of the knowledge gaps I just mentioned and because the rate of fibrinolysis is less than 5% when TEG and ROTEM are used. Still, even in the United States, we may be giving TXA to patients who do not need it. We may even be harming these patients through exacerbation of fibrinolytic shutdown.

H&O What other trials have been conducted?

MW A 2010 study by Zufferey and colleagues published in the *British Journal of Anaesthesia* showed an increased incidence of VTEs in patients with an acute hip fracture who were given TXA. This finding was supported by the results of the retrospective, observational MATTERs study (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation), which was published in 2012. This study of 896 patients with combat injuries found a significant mortality benefit and less use of blood in patients who received TXA, but it also found a 9- to 12-fold increase in the VTE rate.

A retrospective observational study by Swendsen and colleagues of 126 patients with trauma found a mortality benefit with TXA but an increase in VTE. On the other hand, Valle and colleagues also conducted a retrospective observational study of 1217 patients with trauma and found increased mortality with TXA—possibly because of the rapid administration of factor-diluting fluids with TXA administration and the immediate availability of emergency surgery at the urban trauma center in Miami, where time to the operating room was 19 minutes and time to blood transfusion was 7 minutes. Therefore, most of the time TXA was administered after blood transfusion in the operating room. Cole and colleagues from the United Kingdom who were early adopters of the ubiquitous use of TXA in trauma conducted a prospective cohort study of 385 severely injured patients; TXA reduced mortality only in those with severe injury and shock. As a result, they recommend the use of TXA only for patients in shock in mature trauma systems, where patients have immediate access to trauma centers.

Thus, we can see that TXA has a mortality benefit in patients with trauma in most cases, but it does not affect transfusion rates and seems to increase VTE. The Swendsen study also showed a trend toward an increase in acute kidney injury.

I have no problem with giving TXA to all the people who really need it, but we must be aware of the need for VTE prophylaxis in these patients.

H&O What other trials are being undertaken?

MW Several trials are ongoing in the United States and in Australia. The PATCH (Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Haemorrhage)-Trauma trial is a 4-year, 1200-patient multicenter trial that is ongoing in Australia and New Zealand. It is testing the effect of TXA in injured patients.

Another ongoing trial is STAAMP (Study of Tranexamic Acid During Air Medical Prehospital Transport), which is enrolling approximately 5000 patients with hypotension and tachycardia from level 1 trauma center air medical transport programs.

H&O In light of all this information, what approach do you recommend for treating patients with severe traumatic hemorrhage?

MW I favor the approach spelled out by Napolitano and colleagues in the *Journal of Trauma and Acute Care Surgery*, in which anyone with a systolic blood pressure below 75 mm Hg receives TXA, and TEG or ROTEM is used to guide subsequent dosing.

H&O Is there anything you would like to add?

MW Trauma-induced coagulopathy is an orphan disease that is often undertreated because many physicians caring for trauma patients do not recognize it as a common form of acquired coagulopathy. The concept of fibrinolysis in trauma is not an on/off phenomenon; rather, it is a spectrum, and patients can go from a hypercoagulable to a hyperfibrinolytic state and vice versa in minutes or even seconds. Therefore, the great challenge is to find a test that will allow the clinician to detect patients with clinically significant fibrinolysis. Right now, although they are imperfect, the best tests we have are TEG and ROTEM. These tests may lack sensitivity, but they do help us identify patients who have fibrinolytic shutdown after trauma. This is an important concept because patients with no natural fibrinolysis are in a hypercoagulopathic state and may not need TXA.

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Suggested Readings

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