

Advances in Hematology

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*Current Developments in the
Management of Hematologic Disorders*

Alternative and Topical Approaches to Treating the Massively Bleeding Patient

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When do hemostatic agents enter the treatment of massively bleeding patients?

In treating massively bleeding patients, surgical hemostasis is the most important aspect to consider. If a patient has a severed blood vessel, or other such problem, no hemostatic agent will be effective on its own. These agents are used as an adjunct to pressure and surgery. They can decrease the transfusion requirement and allow for a better surgical field.

What types of hemostatic agents are available?

There are several varieties of hemostatic agents. The most commonly used are blood products such as platelets, fresh frozen plasma (FFP), cryoprecipitate (for low fibrinogen), and clotting factor concentrates (recombinant or pathogen-safe, plasma-derived concentrates for patients with clotting factor deficiencies). Prothrombin complex concentrate, a bypassing agent used in hemophilia A with inhibitors, has been reported to rapidly reverse the anticoagulation effect of warfarin, and has been used for the treatment of bleeding associated with warfarin overdose. More recently, there has been interest in the use of recombinant activated factor VII (rFVIIa; NovoSeven [NovoNordisk]) for the treatment of bleeding episodes in nonhemophilic patients. While rFVIIa is approved by the US Food and Drug Administration (FDA) for use in treating bleeding episodes in hemophilia with inhibitors, its compassionate use in the treatment of uncontrolled hemorrhage in nonhemophiliacs is considered off-label. Nontransfusional agents include serine protease inhibitors such as aprotinin, and antifibrinolytics such as aminocaproic acid or tranexamic acid that are used during surgery. Topical hemostatic agents that may decrease transfusion requirements in patients experiencing excess bleeding are also available.

How are the topical agents classified?

The FDA classifies these agents as absorbable and nonabsorbable. The absorbable agents are those that are absorbed within the body. Some of these are effective and some are not, and some are associated with side effects. The nonabsorbable agents are applied on the surface and do not become

absorbed. These agents are made of cellulose and other nonabsorbable fibers. Another useful way to classify these agents is by sealants (liquid adhesives), dressings (solid matrix), and a third category of new materials now being developed.

What are the currently available sealants?

The most commonly used sealant is a fibrin sealant called Tisseel VH (Baxter). It is vapor heated and contains human fibrinogen, human thrombin, bovine aprotinin (to slow down clot dissolution by plasmin) and calcium chloride. Fibrinogen is a clotting protein that is converted by thrombin into fibrin in the body. Fibrin is the lattice that forms with a clot, in which platelets and red blood cells become trapped. To apply this sealant, 2 syringes are used, one with thrombin and the other with fibrinogen. When these are squirted into the site of injury, a clot forms.

Topical thrombin is another type of sealant, and uses bovine thrombin. It is available as a spray or a lyophilized powder with diluent. Just as with the fibrin sealant, the thrombin in this sealant converts fibrinogen in a person's blood into fibrin. The drawback of any animal or human source of products is the potential risk of transmitting pathogens.

There are also sealants made out of nonprotein materials, called cyanoacrylate sealants. These sealants are made from human or nonhuman material.

What different types of dressings are available?

The dressings employ a solid matrix that is applied onto the wound. Some of these matrices are made from protein materials (human or animal), and some from nonprotein materials. The most common type of protein dressing is the microfibrillar collagen called Avitene (Daval). The American Red Cross manufactures a biodegradable fibrinogen bandage. Once applied, the fibrinogen begins to degrade and a clot is formed. Other dressings include Hemarrest (Clarion), TachoComb (Nycomed), and Chitosan (HemCon), which is made from shrimp protein. With all of these products, the aim is to form fibrin.

There are several types of nonprotein dressings that expand across the surface of the site of injury. This type of dressing causes the blood elements to concentrate to form a clot, basically acting as a surface on which the clot can form. Rapid Deployment Hemostat (Marine Polymer Technologies) is a nonprotein dressing made from algae. Another hemostatic dressing is made of oxidized cellulose. The hemostatin bandage is made of propyl gallate, and TraumaDex (Medafor) is made of potato starch. Starch itself can expand, can therefore make an effective dressing. Another type of dressing, Sorbstace (Hemostace), is made of aluminum sulfate, and cellulose itself, an inert material, is also used.

What is the third category of topical agents you mentioned?

In this category are zeolite (QuikClot, Z-Medica; a granular powder) and Urgent QR and Nosebleed QR. According to Commander Rhee of the US Army, soldiers in Iraq carry packets of zeolite. Because of the nature of the fighting, injured soldiers are often trapped and unable to rapidly return to their base for advanced surgical treatment. Open wounds need to be treated immediately to prevent further blood loss. Zeolite can be poured directly into a major wound and pressed to prevent exsanguinations.

Other agents for topical use include Urgent QR and Nosebleed QR (Biolife). These are made of a hydrophilic polymer that forms an artificial scab upon contact with blood. They are available as nonprescription agents and are either applied to the bleeding site or as a swab for nosebleeds.

What are the potential hazards with zeolite?

The FDA recently issued a warning that some absorbable hemostatic agents could swell and cause paralysis and nerve damage due to compression. Agents such as zeolite produce heat, potentially reaching the level of third-degree burns. Hence, zeolite should not be used in closed wounds. The potential for pathogen transmission (such as prion disease) remains with the use of animal- and human-derived products. Topical thrombin may be associated with the development of inhibitory antibodies to factor V and thrombin.

How should one choose a hemostatic agent?

It depends on the type of bleeding and the location of the patient. Clearly, pressure and surgery may be life saving. For uncontrolled hemorrhage, rFVIIa can be used (with permission and clear understanding by the patient/legal guardian that this is an off-label indication). This agent can also be combined with other approaches such as antifibrinolytics. Physicians in Israel are very experienced in the use of rFVIIa for uncontrolled hemorrhage, and many emergency medical technicians have rFVIIa available in the ambulances. We hope that a clinical trial of rFVIIa for trauma patients will be conducted in the United States so that its use for this indication can be approved. FFP in combination with topical agents may be effective, although there have been no clinical trials to establish its hemostatic efficacy. Clinical trials comparing the efficacy of various hemostatic agents that may help us determine which agents are most effective are lacking.

Is it difficult to conduct clinical trials of hemostatic agents?

While not impossible, the individual variability of patients makes such trials somewhat difficult. Clinical trials of this kind would require participation of surgeons, hematologists, blood bankers and pharmacologists. Traditionally, hematologists have not actively participated in trauma teams. This is unfortunate, since hematologists may bring to the team expertise regarding availability, safety, efficacy and expense of newer transfusion-sparing agents, and guide surgeons, pharmacists, and blood bankers in the use of these agents.

Clearly there is a need for trials to determine efficacy and safety of topical hemostatic agents. The data currently available are derived from pig and other animal models, with case reports of their use in humans. The current worldwide threat of terrorism and the potential of civilian and military injuries make it increasingly important to conduct these studies.

During situations of a massive hemorrhage there is often a state of urgency. To focus on a clinical trial in the midst of a life-and-death situation is extremely difficult, and requires very dedicated people. However, I do think that such studies are possible. A study of rFVIIa for intracerebral hemorrhage was recently completed, and demonstrated that the transfusion requirement was decreased with the use of this agent.

Are there age-appropriate choices when it comes to selecting a hemostatic agent?

Yes and no. Volume is a major consideration in children as well as in individuals with coagulopathic bleeding following trauma. In such situations, an effective, low volume, inexpensive product is most desirable. Barring case reports, data in children regarding the use of various hemostatic agents are virtually nonexistent. There have been occasional reports of the use of some hemostatic agents in children undergoing tonsillectomy and adenoidectomy, that showed minimal blood loss, however there are no studies comparing one agent with another. As far as I know, there is no clear understanding about whether a dressing or sealant or other agent is best for older or younger patients.

Suggested Reading

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