Building Better Bandages

New dressings include natural clotting agents

By JOHN TRAVIS

When Martin MacPhee talks about his research, he shows a plate from the British Museum in London that depicts a scene from the Trojan War. Unrolling a cloth bandage, Achilles is trying to stop a comrade's bleeding.

The care of life-threatening blood loss has not improved much over the centuries, notes MacPhee, an investigator at the American Red Cross' Holland Laboratory in Rockville, Md. Physicians faced with hemorrhaging today still try to stop it by covering the wound with gauze or bandages, applying pressure, and hoping the body's natural ability to form clots will stem the flow of blood.

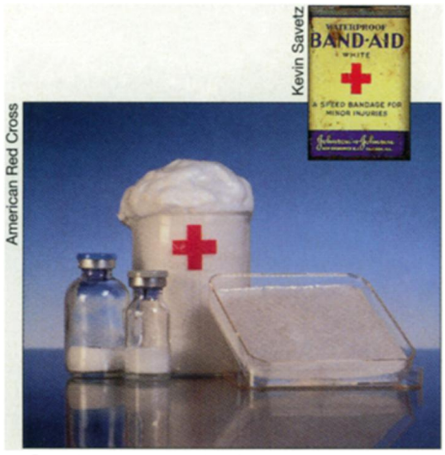
That's often a vain hope. Each year in the United States, around 50,000 people bleed to death due to gunshot wounds, accidents, or other causes. The problem becomes even more acute where it's difficult to get a wounded person to a hospital. "About half of all soldiers who die bleed to death, the majority of that occurring on the battlefield," says MacPhee.

Such statistics have prompted scientists to create a high-tech version of the traditional bandage. Impregnated with concentrated amounts of the natural proteins that form blood clots, the new dressings represent active instruments of healing instead of passive pieces of cloth. Moreover, they may foreshadow clot-forming powders a person will simply spray onto a bleeding wound. "We're trying to reinvent the way we treat trauma and hemorrhaging," says MacPhee.

"We have spent the last 7,000 or so years trying to put a clamp of some sort on a bleeding vessel," notes Kenneth L. Maddox of the Baylor College of Medicine in Houston, former president of the American Association for the Surgery of Trauma. "The concept [of bandages with clot-forming proteins] and the preclinical data on them are very exciting."

About a decade ago, a former battlefield physician was chatting with a colleague when the idea of an active bandage struck him. John Hess had been complaining about wartime medicine. From his experience in the Korean War, he knew that many wounds would not be fatal if medics could just stop the bleeding.

"You see horrible cases of trauma," says Hess, "and one of the most frustrating things is not being able to do anything about them. The more fluids you put in people, the faster they bleed."



Coming soon to the first-aid kit, which has changed little over the years: The fibrin foam and bandage, shown with vials of thrombin and fibrinogen.

Hess and his friend began to muse about ways to quickly stop blood flow. The body is quite adept at stemming small-to-moderate bleeding. Through an intricate clotting cascade, it ultimately manufactures a fine mesh of a substance called fibrin. This protein forms when the enzyme thrombin cuts up another protein called fibrinogen. The fibrin molecules align in long strands, and another enzyme, factor 13, finishes the job.

Factor 13 "cross-links the fibrin strands together to form a net, and that net becomes dense enough with time that red blood cells can't go through it," explains William Drohan of the American Red Cross.

Hess knew that scientists had purified blood-borne fibrinogen and thrombin into soluble powders. "What happens if you just push the dry powders into a wound?" he wondered. Hess presumed that water in the blood there would dissolve the two proteins and stimulate clotting.

When he tested the concept on wounded arteries in animals, it worked dramatically well. By 1993, Hess was working with the American Red Cross, which was independently developing what it calls fibrin sealant bandages.

The concept dates back several decades. In 1941, Japan's surprise attack on Pearl Harbor left many sailors badly burned. When physicians removed damaged tissue, they employed human fibrinogen and cattle thrombin to stem blood loss and glue skin grafts in place.

The fibrin clot has a natural tendency to stick to wounds, notes Drohan, because factor 13 also cross-links fibrin strands to molecules exposed in damaged tissue.

After Pearl Harbor, however, fibrin wound sealants got a bad reputation. "Fibrinogen is isolated from plasma by a method that tends to copurify with a lot of viruses," notes Drohan. To avoid transmission of viruses, the Food and Drug Administration pulled fibrin sealants off the U.S. market in 1978.

Within the past 10 to 15 years, however, scientists have devised ways to inactivate any viruses that may tag along with fibrinogen. European physicians quickly embraced that advance. Many now routinely use commercially produced fibrin sealants to control mild-to-moderate bleeding during surgical procedures.

While some U.S. surgeons have been concocting their own fibrin sealants for years, FDA approved a commercial fibrin sealant for surgery only in 1998.

Applying these surgical wound sealants is still cumbersome. Vials of freeze-dried thrombin and fibrinogen powders must be first warmed, their contents then dissolved in separate measures of water, and the solutions finally placed in a double-barrel syringe so that the clotting agents combine as they squirt onto a bleeding cut. "It does take time, anywhere from 20 minutes to an hour," notes MacPhee.

Furthermore, because of the expense of obtaining the proteins, each vial has traditionally contained relatively little thrombin or fibrinogen. The amount of fibrin created by this approach is not nearly enough to stop massive bleeding from large wounds.

In contrast, each 4-inch-square bandage being developed by the Red Cross and Army contains more thrombin and fibrinogen than is present in an average person's whole body. "We're simply providing a higher concentration [of the clotting agents] at the site of injury than would normally be there," explains Drohan.

To produce the fibrin bandages, the researchers begin with a cloth made of biodegradable material and then saturate it with thrombin, fibrinogen, and factor 13 purified from human blood. The resulting bandages are brittle until they

get wet, and then they become "magnificently flexible," says MacPhee.

"It's like holding a piece of Styrofoam at first. As soon as you press it into a wound, it just kind of melts and takes on the shape of the tissue," he reports.

Hess, now at the Walter Reed Army Institute of Research in Rockville, Md., and John Holcomb of William Beaumont Army Medical Center in El Paso, Texas, have spearheaded initial testing of the bandages. Like Hess, Holcomb's interest stems from being an Army medic. In Somalia, when U.S. soldiers were ambushed in Mogadishu, Holcomb saw several die from blood loss, including one who received more than 40 pints of blood.

The physicians have tested the fibrin bandages on goats with injuries similar to gunshot wounds. In the January 1998 ARCHIVES OF SURGERY, they reported that goats treated with the fibrin bandages had about one-third the blood loss of animals receiving normal dressings. The fibrin strategy also maintained the goats' blood pressure.

Furthermore, the researchers have tested fibrin bandages on severe liver injuries resembling those sometimes suffered in car wrecks. These grade-V injuries are fatal more than 70 percent of the time, primarily because of bleeding from large blood vessels in the liver.

Physicians currently treat such injuries by opening the abdomen, stuffing gauze onto the damaged liver, and sewing the abdomen closed to keep pressure on the wound. They can then only hope that clots will form in time.

When Holcomb and his colleagues used fibrin bandages to treat four pigs with grade-V liver injuries, the animals had, on average, 51 percent less blood loss than swine treated with normal dressings, the physicians report in the January JOURNAL OF TRAUMA. Most of the pigs treated conventionally died, while all the animals receiving fibrin bandages survived. One even recovered from surgery so quickly that it escaped the operating room and had to be chased down by Army Rangers.

When the pigs' livers were examined more than a month after the injury, the organs seemed healthy and had no visible scars. The fibrin clot had also disappeared as expected; the body's enzymes break up fibrin over time.

Hess predicts that it will be about 3 years before fibrin bandages make their widespread debut. The scientists need about a year to hone the manufacturing process, another year to test the bandages on people, and a final year to negotiate the FDA review process, he says.

Although no inappropriate clots have formed during the animal testing, the researchers need to confirm in people that the massive amounts of clotting agents in the bandages don't trigger clots outside the wounded area. Such clots could cause heart attacks or strokes, for example.

The researchers don't plan to stop at just fibrin bandages. They've started to develop a foam that mixes the clotting agents with carbon dioxide and water. An emergency medic might shoot such a foam into an injured person's abdominal cavity in order to stop internal bleeding immediately. "It's like Fix-A-Flat for people," jokes MacPhee.

The Red Cross is also developing a spray can that shoots out a fine mist of the dry clotting agents. As in Hess' original concept, this powder would dissolve into a wound's moisture and start a clot. Such a tool might prove useful for large wounds or burns. "We envision the soldier of the future will carry a bandage or two, a dry powder [in a spray can], and the foam," says Drohan.

All these applications demand considerable amounts of the clotting agents, and therein lies a challenge. Scientists now purify the proteins from blood, a process both laborious and expensive. Although hesitant to make an estimate before manufacturing expenses are known, MacPhee acknowledges that one large fibrin bandage might initially cost several hundred to more than a thousand dollars.

To lower that price, the American Red Cross plans to genetically alter animals such as goats or cows so they will secrete large amounts of human fibrinogen or other clotting agents into their milk. Ultimately, says Drohan, the organization would like fibrin bandages to be cheap enough so that an average person can buy at least one for emergency use.

Meanwhile, scientists are exploring whether fibrin sealants may have uses beyond halting blood loss. Creating new bone is one possible application. The American Red Cross has been exploring whether transplants of bone minerals taken from cadavers can prompt new bone formation. When mixed with a fibrin gel, the bone minerals become an easily molded putty. The scientists have placed this material in animals and successfully created square, triangular, and doughnut-shape pieces of bone within a month.

Even before its research on bandages began, the team was studying whether fibrin could be used to deliver drugs. Fibrin has all the attributes of a perfect delivery device, contends MacPhee. It's naturally adhesive and absorbed safely by the body.

Working with Christopher J. Woolverton of Kent (Ohio) State University, MacPhee and his colleagues have mixed insoluble antibiotics with the clotting agents to create a fibrin gel that slowly releases the drugs for nearly a month. They've also incorporated various natural factors that promote cell growth and so may help wounds repair themselves.

Perhaps the most provocative project with fibrin would enlist it to fight cancer. When confronted with ovarian cancer or other solid organ tumors, physicians normally try to surgically remove as much of the tumor as possible, a procedure called debulking. They later administer chemotherapy and radiation to the patient. Yet tumors often recur near the original site.

The Red Cross researchers have started to examine whether anticancer compounds such as taxol might be delivered by fibrin, which would be applied during the debulking operation. The fibrin would stick to the tissue exposed by the surgery and slowly release drugs at what is the most probable location for tumor regrowth. In preliminary animal tests, the strategy has helped prevent the recurrence of tumors, says Drohan.

He and his colleagues envision fibrin being as helpful in the war on cancer as they predict it will be on the bloody battlefield. □

In the Navy, algae tackles bleeding

While the Army has been working with the Red Cross, the Navy has approached the problem of treating bleeding with, naturally, a nautical tack. The service is sponsoring an effort to develop bandages derived from a substance made by a marine microalga.

This single-cell organism extrudes a polymer called poly-*N*-acetyl glucosamine. The fibers, which radiate out from the cell, appear to help the alga maintain an ocean depth conducive to photosynthesis.

The substance is similar to other natural polymers that have previously been considered for use as bandages. However, researchers can easily obtain large amounts of pure poly-*N*-acetyl glucosamine by growing alga in the laboratory. Marine Polymer Technologies in Danvers, Mass., has already earned FDA approval for a surgical patch made from the polymer.

"It sticks right to neighboring tissue and seals off the wound. The bleeding stops instantly," says John Vournakis of the Medical University of South Carolina in Charleston, who is a vice-president at the firm.

The Office of Naval Research first took an interest in the polymer when Vournakis showed a retired Navy admiral how bandages made from it could control bleeding. Unlike the fibrin bandages, poly-*N*-acetyl glucosamine patches do not contain clotting agents. They merely provide an impermeable barrier to blood cells and give the body time to form its own clots.

These dressings have already been tested on people. "At the moment, our material is a lot cheaper [than fibrin bandages]," says Vournakis. "We think there are niches where our product may be more suitable." —*J.T.*