Surgery Without Sutures

Glues may solve some sticky problems in medicine

By STEFI WEISBURD

"Scalpel! Forceps! Glue!" In the operating rooms of the future, surgeons may routinely use medical adhesives in place of sutures and staples, especially in very delicate microsurgeries where sutures and staples can damage tissue. European surgeons already use an adhesive made of natural blood-clotting agents to bond together the fine bones and tissues in the inner ear while they heal. In the United States, researchers are now involved in clinical trials of both natural and synthetic adhesives that they hope will eventually be approved for use in everything from skin grafts to cornea repair to nerve surgery.

Physicians at the Hospital of the University of Pennsylvania (HUP) in Philadelphia announced last month that they have developed an improved version of the European blood-clotting adhesive and have begun to use it in a 100-patient, two-year study of ear surgeries.

According to Leslie Silberstein, director of the hospital's blood bank, the "autologous fibrinogen adhesive" consists of the human protein fibrinogen and bovine (cow) thrombin, which induces the fibrinogen to bond to surfaces. Unlike the European compound, which is made of fibrinogen from a donor pool, the HUP adhesive contains fibrinogen that comes from the patient's own blood, thus eliminating the risk of transmitting infectious diseases such as hepatitis and AIDS, notes Silberstein.

"The method we've devised to prepare [this adhesive] has not been used before," he says. "We've chosen it because we can prepare it from as little as 20 milliliters of the patient's plasma – that's about two small tubes of the blood."

By controlling the amount of thrombin in the mixture, surgeons can vary the time it takes a clot to form from several seconds to two minutes. The adhesive is injected into the ear through a thin needle. According to Robert Weisman, an ear, nose and throat surgeon at the University of Pennsylvania School of Medicine and director of the study, it is being used to hold in place pieces of soft tissue – such as tissue grafts for repairing holes in the ear drum – and to bond bone together.

The adhesive should also guarantee that synthetic implants or cartilage, which surgeons often wedge into the ear to replace bones and make other repairs, stay in place. With it, Weisman's team hopes to pull the present 60 to 65 percent success rate of conventional ear surgeries up to 90 percent.

So far surgeons have used the adhesive in about 10 operations. "Our results have been favorable," says Weisman. "If nothing else, I think we are finding that it may make the surgery easier to perform. . . . But we're going to wait until we have a large number of patients [before we come to any strong conclusions]."

Weisman believes the fibrinogen adhesive could find use in other kinds of delicate operations that are performed in the United States tens of thousands of times each year. In the April PROCEEDINGS OF THE MAYO CLINIC, for example, Patrick M. McCarthy and his colleagues at Mayo Clinic in Rochester, Minn., report success in using a similar fibrinogen adhesive in one patient to repair a hole in the large intestine. Silberstein notes that, in general, studies are needed to determine the extent to which the adhesive could be used in areas that are in direct contact with blood flow, because blood can dissolve the adhesive.

In addition to natural adhesives, synthetic compounds for surgery and other medical practices have long interested physicians. According to Charles DeSmet of BioNexus, Inc., in Raleigh, N.C., thousands of papers were written in the 1960s on the possible medical uses of methyl cyanoacrylate, a compound that was first synthesized in 1955 by researchers searching for a polymer with which to make airplane windshields. Methyl and ethyl cyanoacrylates are commercially known today as Super Glue and Krazy Glue.

Interest in developing medical products from the adhesive waned, says DeSmet, because methyl cyanoacrylate is sometimes cytotoxic, damaging cells it is supposed to help repair. Nonetheless, other researchers note that for some kinds of eye surgeries, the need for an adhesive has been so great that surgeons regularly use cyanoacrylates – which are produced in Germany and brought into the United States through Canada – even though the U.S. Food and Drug Administration has not approved such use.

Last fall, DeSmet's company received an orphan grant – a grant to explore the use of a product not yet considered profitable enough to warrant manufacturing – from the FDA to produce and conduct tests on butyl cyanoacrylate and other cyanoacrylate compounds that DeSmet says are much less cytotoxic. According to DeSmet, this was the first orphan grant awarded for the testing of a medical device.

DeSmet notes that ophthalmologists at Duke University in Durham, N.C., have begun clinical trials of the compound in treating punctured or ulcerated corneas of the eye. And at Walter Reed Army Medical Center in Bethesda, Md., neuroradiologists are planning to try using butyl cyanoacrylate to block off brain arteries that are weak and ready to rupture. Researchers expect the glue to be most useful for high-risk patients who are not candidates for the standard microsurgery procedures.

DeSmet says he's talked to physicians who have used or are interested in using cyanoacrylate adhesives for a variety of purposes, including cosmetic surgery, the repair of varicose veins, gum surgery and orthopedics. BioNexus manufactures a cyanoacrylate compound used by veterinarians as a topical bandage, and DeSmet says the U.S. military, which used an aerosol cyanoacrylate for covering wounds of soldiers in Vietnam, has also expressed interest in the company's improved cyanoacrylate adhesives. In addition, BioNexus has FDA approval to explore the use of the compound in sterilization procedures that block off the

fallopian tubes of women.

Because alkalinity causes the cyanoacrylate adhesives to solidify, DeSmet notes that it may not work well in some parts of the body, such as the acidic gastrointestinal tract. But the advantage of synthetic adhesives "is that they can be controlled so well," he says. "They can be produced in large quantities and we can change their properties – such as viscosity and setting time – very easily by manipulating chemistry."

Another advantage of synthetic adhesives, adds Weisman, is that they don't have to be prepared in advance of an operation. However, the disadvantages of synthetic adhesives in the past, he says, have been that they are too brittle when dried (although DeSmet says brittleness is no longer a problem) and that they hold a risk of being rejected by the body as a foreign object. These factors, coupled with the cytotoxicity of previous synthetics, were part of the impetus for developing the fibrinogen adhesive, he says.

The past problems with cyanoacrylate synthetics have motivated other researchers as well to look for alternatives. One especially promising approach is being followed by scientists at BioPolymers in Farmington, Conn., who are taking their cues from nature. They have discovered that an ideal adhesive for medical applications is a protein secreted by marine mussels when the animals attach themselves to rocks, sand and other objects on the seafloor.

One of the reasons it's taken so long to develop satisfactory synthetic adhesives, says Christine Benedict, vice-president for research and development, has been that "there were formidable barriers to understanding how biological systems attach." It wasn't until 1981, after scientists had worked on the problem for 20 years, that J. Herbert Waite, one of the founders of BioPolymers, worked out the biochemistry of the mussel adhesive, she notes.

According to Benedict, BioPolymers is now working to make a synthetic analog of the natural mussel adhesive and plans to apply to the FDA this year for clinical ophthalmological trials.

Unlike the cyanoacrylates, says Benedict, the mussel adhesive "forms a porous matrix in between two pieces of tissue so that healing can occur through and around it. And it doesn't harm the cells on either side of the adhesive."

But the biggest selling point of the mussel adhesive for Jeffry Robin, an ophthalmologist conducting animal research on the adhesive for BioPolymers, is that the material works in an aqueous environment – a property, he says, that ophthalmologists have long awaited.

"People have been eager to find alternatives [to cyanoacrylates], particularly for larger-size corneal perforations, where the fluid inside the eye is gushing outside and you can never get it dry enough for the cyanoacrylate to polymerize," says Robin, who is at the University of Illinois at Chicago. "It's a very exciting area, and certainly in ophthalmology, we're right up there with orthopedics and cardiovascular surgery in terms of having the most immediate uses for an aqueous, effective adhesive."

In addition to closing corneal holes that are too large to be sewn together, Robin says the mussel adhesive might be used for cataract incisions, eye muscle surgery and perhaps retinal attachment. The use of adhesives in eye surgery in general, he adds, may reduce the number of astigmatisms that result from the concentrated pressure to the eye from sutures.

Regardless of which type of adhesive turns out to work best in various surgeries, everyone agrees that the need for such adhesives is great. "I think there is a trend for more and more microsurgery to be performed," says Weisman, "and I think there will be more applications [for adhesives] as microsurgery expands." □