Hemostatic Effectiveness of Fibrin Glue Derived from Single-Donor Fresh Frozen Plasma

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ABSTRACT Fibrin glue derived from pooled human blood is an effective sealant for high-porosity vascular grafts and a valuable topical hemostatic agent in heparinized patients. Use of this agent in the United States is prohibited because of potential transmission of hepatitis B, acquired immunodeficiency syndrome, and other serologically transmitted illnesses. We have developed a cryoprecipitation technique that allows preparation of fibrin glue from single-donor fresh frozen plasma. Use of this agent presumably entails no greater risk of disease transmission than intravenous administration of single-unit fresh frozen plasma. This report describes our early clinical experience with this material.

Fibrin glue was used as a sealant for porous woven Dacron tubular prostheses and cardiovascular patches in 19 patients. The fibrin glue sealant has also been employed to control bleeding from needle holes and small anastomotic tears in 22 patients. No patient in this series had a bleeding complication from a suture line or graft treated with fibrin glue.

This experience indicates that like fibrin glue from pooled blood, fibrin glue from single-donor plasma is effective as a graft sealant and topical hemostatic agent. Preparation of fibrin glue from single-donor plasma is simple and economical, and may provide cardiothoracic surgeons in the United States with a widely available, valuable hemostatic adjunct.

The efficacy of fibrin glue as a vascular graft presealant and surgical adjunct to control bleeding has been well documented in Europe where it has been used for years in cardiovascular surgery [1-8]. The European glue is a commercially available fibrinogen concentrate (Tissucol, Immuno AG, Vienna, Austria) prepared from pooled donors. In 1978, the Food and Drug Administration revoked licenses for clinical use of pooled fibrinogen [9] because of the risk of hepatitis B transmission. Therefore, Tissucol is not approved for use in the United States. The appearance of acquired immunodeficiency syndrome (AIDS) [10] has added to concern that use of blood products derived from pooled donors carries unacceptable risks.

We have developed a fibrin glue made from cryoprecipitation of single-donor fresh frozen plasma [11]. Use of this fibrin glue entails no greater risk of disease transmission than intravenous administration of single units of fresh frozen plasma. This report describes our early clinical experience with Columbia Fibrin Glue.

Material and Methods

Preparation of the glue has been described previously [11]. Thawed single units of fresh frozen plasma screened for hepatitis B and syphilis by the blood bank are divided into 50-ml aliquots, which are then refrozen at -80°C for at least eighteen hours. After slow rethawing at 4°C, the material is centrifuged at 1,000 × g for fifteen minutes. The yellow precipitate contains concentrated fibrinogen, which may be used for up to four days if kept at 4°C. Alternatively, the fibrinogen concentrate can be refrozen and stored for as long as one year [12]. One unit of fresh frozen plasma yields 8 to 10 ml of fibrinogen concentrate, enough for 1 to 4 patients. The method is easy to learn, reproducible, and economical.

The application techniques have been detailed by us [11] and others [6, 7]. Porous grafts are presealed by application and massage of the fibrinogen concentrate (preglue) into graft interstices, followed by similar application of topical thrombin solution (Thrombinar, Armour Pharmaceutical Co., Kankakee, IL) (Figure). For sealing vascular suture lines, it is preferable to apply the glue on a matrix of pledgets of either Gelfoam (absorbable gelatin, The Upjohn Company, Kalamazoo, MI) or Avitene (microfibrillar collagen hemostat, Alcon Surgical, Fort Worth, TX) wafers. Gelfoam was used in most of the patients in this series, but recently we have been more impressed with the efficacy of Avitene wafers. Hemostatic control for large arterial suture lines is obtained best by applying glue before removing the cross-clamps. The glue must be applied in a dry field. Suction should not be used for several minutes until the glue has time to gel. On suture lines of smaller vessels, such as saphenous vein graft coronary artery anastomoses, fibrin glue impregnated on Avitene wafers is applied and activated by topical thrombin. The site is covered by a dry sponge, and firm pressure should be applied for three minutes. As with any surgical maneuver, a good result depends on proper use gained by experience. The
Woven Dacron patch preclotted with fibrin glue is sutured in place as an onlay in a modified Fontan procedure. The suture line is then covered with preglue and topical thrombin, which form the suture-line seal.

glue is no substitute for careful surgical technique and well-placed sutures.

Between May and October, 1984, fibrin glue was used in 41 operations. In 19, the glue was used to preseal woven Dacron tubular prostheses and cardiovascular patches. In 22 instances, the glue was employed to control bleeding from needle holes and small anastomotic tears (Table). Thirty-eight of the 41 patients were fully heparinized and on cardiopulmonary bypass during the operative procedure. The three exceptions included repair of coarctation for the aorta (1 patient) and resection of thoracic aortic aneurysm (2 patients).

Results
Initially the glue was used to pretreat vascular prostheses and the adjacent prosthetic suture lines. As experience was gained with the glue and its impressive hemostatic action was appreciated, the uses of the glue rapidly expanded.

No patient in this series had persistent bleeding intraoperatively. There was one episode of excessive postoperative hemorrhage defined as bleeding in excess of 10% of blood volume in two hours or a total of 20% of blood volume at any time. This episode occurred in the only patient in this series who required reexploration for hemorrhage. Bleeding from the right atrial cannulation site, which had not been treated with fibrin glue, was found at reoperation in this patient, in whom right heart failure with elevated right atrial pressure developed after patch closure of an acute posterior ischemic ventricular septal defect.

There was no identifiable morbidity associated with the use of the glue. No hypersensitivity reactions were observed. There were no episodes of disseminated fibrinolysis or coagulopathy. With a follow-up of three to seven months, no cases of hepatitis or AIDS have been noted.

Comment
The hemostatic effectiveness of multidonor fibrin glue has been documented extensively [1-7]. The experience reported here indicates that like fibrin glue prepared from pooled blood, fibrin glue extracted from single-donor fresh frozen plasma is similarly effective as a graft sealant and topical hemostatic agent in patients undergoing cardiovascular surgical procedures.

Knitted prostheses were not evaluated in this preliminary report. Previous work with the European glue suggests that when highly porous knitted grafts are pre-treated with the fibrin sealant, they are no more thrombogenic, and may be less so, than untreated grafts or those pretreated with blood [1]. The handling characteristics of high-porosity grafts pretreated with fibrin glue are superior to low-porosity prostheses, and fibrin presealing is a simpler technique than preparing grafts by baking with blood, albumin, or plasma. In addition, the superior healing characteristics of high-porosity fibrin-presealed grafts may lower the incidence of late right ventricular conduit obstruction [8].

Certainly, this series demonstrates that pretreatment of porous vascular prostheses with this fibrin glue provides effective graft hemostasis in heparinized patients. Although the glue can be particularly helpful in situations in which suturing may be difficult, it is not a hemostatic panacea. It is not capable of stopping massive arterial bleeding such as gaping aortic suture lines.
With the increasing number of reports from Europe detailing the usefulness of fibrin glue, surgeons in the United States have begun to investigate acceptable substitutes for the unavailable European product. One alternative has been to employ the patient's own plasma as a source of fibrin glue production [12]. Although safe, this method requires the anticipation of the operation and the need for glue two days in advance to draw the autologous blood and prepare the glue in time. Furthermore, the volume of glue that can be extracted is finite, and donation of blood as a source of glue may result in the need for blood transfusion. Finally, the autologous glue is not available in cases of trauma or other emergencies.

A second alternative is to employ standard cryoprecipitate as a substitute for fibrin glue [13, 14]. Although it as been reported to be useful [14], we have found that the volume of cryoprecipitate required is technically cumbersome. In addition, the fibrinogen concentration in cryoprecipitate is quite variable between individual units and is much lower than in our fibrin glue preparation [11, 15].

In this series, 41 patients were treated effectively with fibrin glue derived from single-donor fresh frozen plasma without demonstrable adverse side effects or serologically transmitted infections in short-term follow-up. These results suggest that proper use of this glue could shorten operating time, reduce intraoperative bleeding and the need for blood transfusions, improve the patency of vascular conduits, and potentially save lives.

References

Discussion
DR. ERNST WOLNER (Vienna, Austria): It is now ten years since I first had the opportunity to use the fibrin sealant. The patient required prosthetic replacement of the ascending aorta. The opportunity arose because an institution in Vienna had developed the fibrin sealant at that time, and we received it for testing in animals and human beings.

Since then, thousands of patients have been treated in Europe with this sealant and hundreds of reports have been published about it, reports that more or less confirm the reported data.

Concerning this new preparation, I have two questions. First, is this sealant as effective in making vascular grafts impermeable as the commercial fibrin sealant? This trait is a function of the concentration of fibrinogen, and I suspect that it is a little bit difficult to always get an equal concentration of fibrinogen in your preparation.

Second, do you have any data about the strength of adherence? In other words, what is the pressure required to dislodge your sealant from the surface of a vessel, since this depends on the relation of the concentration in the different components?

Nevertheless, despite my questions, there are some data that the risk of hepatitis is not increased by fibrin sealant, and your sealant seems to have the big advantage of being less expensive.

DR. ROSE: Our glue preparation uniformly renders woven Dacron prostheses impermeable. We have no clinical experience with high-porosity knitted prostheses, but in animal surgical models these grafts are also fully sealed. We have not determined the strength of adherence of our glue; still, it does contain factor XIII, which polymerizes the fibrin generated.

We believe our small-batch, single-unit technique of glue preparation offers an advantage over the large-batch, pooled European technique in that transmissible disease from a plasma donor cannot be spread to a large number of patients.