

A Prospective, Randomized, Double-Blind Trial of the Use of Fibrin Sealant for Face Lifts

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Fibrin sealant imitates the final phase of the blood coagulation process. Fibrinogen is converted into fibrin on a tissue surface by the action of thrombin, which is then cross-linked by factor XIIIa, creating a mechanically stable fibrin network. This fibrin network is thought to reduce the amount of postoperative bleeding by sealing capillary vessels and allowing raw operative surfaces to adhere.

The authors conducted a prospective, double-blind, randomized, controlled trial on the use of fibrin sealant in 20 consecutive patients undergoing bilateral face lifts by the same surgeon. Each patient was randomized for the use of fibrin sealant on either the right or the left side with the contralateral side acting as the control. Total drainage was recorded on each side for 24 hours before drains were removed. The age range of the patients in the trial (all of whom were women) was 44 to 70 years (mean, 55). The side treated with fibrin glue had a median drainage of 10 ml and the control side 30 ml. The Wilcoxon signed rank test shows a significant difference in drainage between sides ($p = 0.002$). The reduction in postoperative drainage could also reduce pain and bruising, increasing patient satisfaction with this procedure. The need for drains may also be obviated. (*Plast. Reconstr. Surg.* 108: 2101, 2001.)

Fibrin sealant has been used for many years and has a wide range of clinical applications for suture support, tissue adhesion, and hemostasis. The physiologic mechanism that creates fibrin sealant was first described by Morawitz in 1905. Since this time, attempts have been made to reproduce this mechanism for clinical use with varying success. In the 1940s a combination of thrombin (artificially added) and fibrinogen from the wound plasma was used for cataract operations.¹ Fibrin sealant was first marketed in 1983. It has been used more widely in Europe than in the United States, and studies have shown fibrin sealant systems to be

efficacious in controlling slow bleeding foci, diffuse oozing, and lymphatic leaks.²

Fibrinogen is a soluble blood component that constitutes 0.2 percent by volume of whole blood.³ On the tissue surface, fibrinogen is converted to monomeric fibrin by the actions of factor XIII, creating a mechanically stable fibrin clot with good adhesive properties. Aprotinin is added to prevent the proteolytic degradation of fibrin. This is the physiologic basis of fibrin sealants.

Beriplast P (Centeon House Market Place, Haywards Heath, West Sussex, United Kingdom) is a tissue sealant and hemostatic agent aseptically prepared by mixing together two reconstituted lyophilizates in two sterile vials that do not require incubation. The reconstituted preparation mimics the final steps of physiologic coagulation. Fibrinogen is converted to fibrin on the wound surface in the presence of calcium ions by the actions of thrombin and factor XIII, all derived from human plasma. A stable cross-linked fibrin clot is formed. Aprotinin is an antifibrinolytic agent that reduces the rate of clot lysis by endogenous plasmin.

For use, the constituents are mixed from two solutions, each of which is loaded into a syringe, one containing fibrinogen, factor XIIIa, and aprotinin, and the other containing thrombin and calcium chloride. The two solutions are mixed when they are sprayed onto the wound to form fibrin.

Fibrin sealant has been used in face lift surgery in the past with good results. Studies have shown that both dressings and drains can be

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avoided,^{4,5} although these were not prospective randomized trials. Face lift surgery is well suited to the use of fibrin glue. A raw surface is created during face lift surgery with the risk of bleeding and hematoma formation. As with all surgery, the patients would like short hospital stays and low associated morbidity such as pain, bruising, and bleeding. These need to be minimized in what is generally a cosmetic procedure, although similar techniques may also be used in facial reconstruction.

PATIENTS AND METHODS

This trial was designed as a prospective, double-blind, randomized, controlled trial with ethical committee approval. Twenty-two consecutive patients were asked to participate in the study, 20 of whom gave informed consent and were recruited into the study. Informed consent involved a discussion with the operating surgeon and an information sheet. Of these 20 patients, all were women and were undergoing bilateral face lifts. All the procedures were carried out in the same hospital by the same surgeon. The surgery was identical in all patients and involved a superficial musculoaponeurotic system (SMAS) plicating face lift without extensive undermining of the SMAS but with undermining of the facial skin.

The fibrin sealant solution was reconstituted in theater from four sterile vials, which are manufactured as two preloaded combination sets (Fig. 1), the first consisting of one vial containing fibrinogen and factor XIII and the other vial containing aprotinin solution. The second combination set contained one vial of thrombin and a second of calcium chloride solution. They are stored in a refrigerator, but when removed remain stable for up to 36 hours. When mixed together, they remain stable for up to 8 hours. Both solutions are drawn up into a syringe and are loaded into the applicator (Fig. 2); as the plungers are pushed simultaneously, the solutions are mixed by the applicator and sprayed onto the wound. The applicator sprays the fibrin sealant onto the wound as a thin layer and therefore allows a relatively small volume (1 ml) of sealant to be used, reducing cost.

During the face lift procedure, after hemostasis was achieved on one side, a sealed envelope was opened to show whether the patient was randomized to the right or left side. Then, 1 ml of Beriplast P was sprayed into the selected wound on either the right or the left



FIG. 1. The fibrin sealant solution reconstituted in theater from four sterile vials, manufactured as two preloaded combination sets.

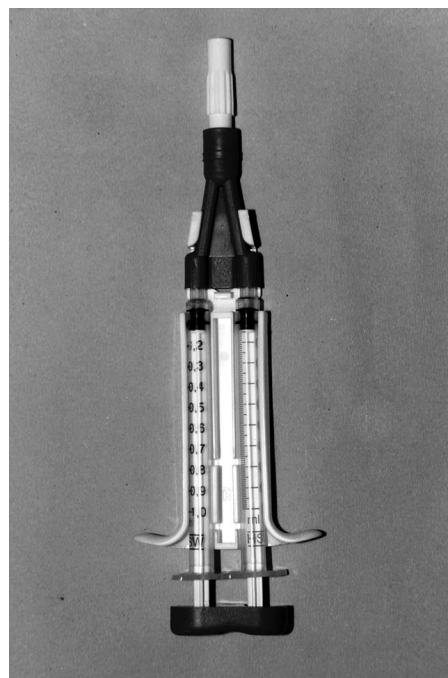


FIG. 2. Delivery system showing the applicator syringe.

before closure of that side. The other side of the face lift was then performed in an identical manner. Both sides were closed in the same way over a small suction drain. Wet and dry dressing gauze was placed over the wound and the dressings secured with two crepe bandages. In each patient, either the right or the left side

received fibrin sealant, with the contralateral side acting as the control.

In the postoperative period, all patients spent the night in the hospital, and the drainage from each side was recorded over the next 24 hours by the nursing staff who were blinded as to the side that contained the glue. The patients were asked for any comments after their surgery, but we did not formally assess their pain scores. Statistical analysis was by the Hospital Center for Applied Medical Statistics using SPSS software.⁶

RESULTS

The patients ranged in age from 44 to 70 years (mean, 55 years) and all were women. The statistical analysis used was the Wilcoxon signed rank test for nonparametric (distribution-free) testing, as the data were not normally distributed. The fibrin sealant side had a median drainage of 10 ml (lower quartile, 5 ml; upper quartile, 20 ml) in 24 hours compared with the control side, which had a median of 30 ml (lower quartile, 20 ml; upper quartile, 47.5 ml). There was a significant difference between the fibrin sealant and the control side ($p = 0.002$) despite the return to theater of one of the patients.

The paired data are displayed in Figure 3, with data arranged by increasing drainage from sealant side. One patient (patient 20) returned to theater from the recovery room with a postoperative hematoma on the sealant side. A single bleeding arterial vessel was identified and ligated. Two patients had equal drainage on both sides, and the remaining patients all had higher drainage from the control side. No other patients required aspiration or reexploration of hematomas. In addition, 6

of the 20 patients (30 percent) voluntarily reported less pain on the sealant side.

DISCUSSION

Fibrin sealant can reduce bleeding and is used by many surgical specialties. The versatility is such that fibrin glue was used in up to 5 percent of all surgical procedures in a U.S. hospital in 1995.⁷ For example, fibrin sealants have been used in liver resection to aid hemostasis,⁸ to seal bronchial and alveolar leakage after pulmonary resections,⁹ and for the endoscopic treatment of bleeding gastroduodenal ulcers.¹⁰ Fibrin sealants have also been used extensively in craniofacial surgery, in particular, to seal dural tears and also for tissue adhesion in endoscopic brow lifts.¹¹

Because the exact composition and delivery system differ between products, it may be difficult to draw parallels between different products¹²; however, we do not believe that the fibrin sealant in our study differs significantly from any other fibrin sealant. All vary in the specific methods of manufacture but rely on the same physiologic process to form fibrin on the wound surface.

As was the case with one of our patients, fibrin sealant is not a replacement for meticulous hemostasis. Although we believe that fibrin sealant reduces capillary bleeding and serous exudate from the operative surfaces, it does not prevent bleeding from small arterial vessels, which can be a cause for postoperative hematomas.

The use of fibrin sealant in an elective cosmetic procedure does raise the ethical consideration as to the use of a material derived from blood products. Fibrinogen, thrombin, and factor XIII are isolated from human plasma. Therefore, there is a theoretical risk of transmission of hepatitis B and C virus, human immunodeficiency virus, and human T-cell leukemia/lymphoma virus type I or II from blood products. A recent study into the risk of transmission of these infective agents found no cases in over 20,000 blood transfusions.¹³

There have also been adverse reactions reported from dural use of fibrin sealants when applied during neurosurgical procedures. Two fatal reactions have been associated with the use of another product because of a severe neurotoxic reaction of unknown cause.¹⁴ This product is therefore only advised for use in liver surgery, for which it is licensed. It is likely that the tranexamic acid in this product was

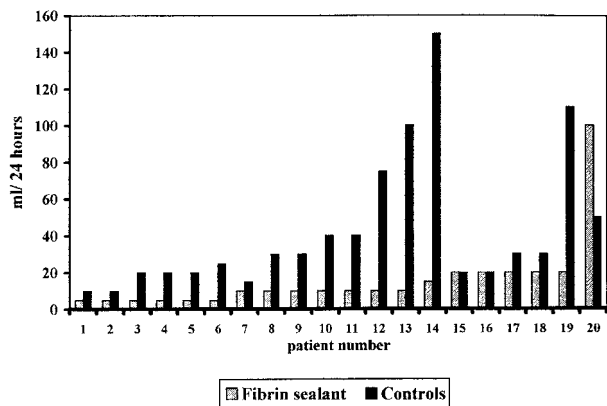


FIG. 3. Graph showing 24-hour drainage: fibrin sealant and controls.

the agent responsible, which is not present in Beriplast P. This contraindication is unlikely to be of clinical relevance for plastic and reconstructive surgeons, as it does not appear to involve peripheral nervous tissue.

Aprotinin is a protein isolated from cattle lungs and acts as an antifibrinolytic agent. There have been safety concerns raised about the safety of products from a bovine source because of infective agents, hence the South American origin of the bovine product, where there have been no reported cases of bovine spongiform encephalopathy. Because the aprotinin is of non-central nervous system origin this should also minimize any theoretical risk. There have been adverse reactions to the repeated use of aprotinin, with five cases of skin reaction reported following 1 million exposures to fibrin sealant. This is thought to be attributable to aprotinin-specific immunoglobulins that can cause skin reaction on re-exposure within a few weeks to aprotinin in fibrin sealants.¹⁵ There are, however, a number of agents that may be used in the future to replace aprotinin.¹⁶

The safety measures used in the production of Beriplast P and other fibrin sealants include screening of plasma donors and donated plasma, inactivation during the manufacturing process, and pasteurization. Since first introduced in 1983, over 1 million patients have received Beriplast P, with no recorded transmission of any pathogens. However, there will always be concern about any blood-derived product, and stringent safety procedures are therefore mandatory.

It is possible to extract fibrinogen from the patient's blood in the perioperative period. One commercially available system uses 120 ml of the patient's blood to produce 4 ml of fibrin sealant,¹⁷ although concentrations of fibrinogen are lower than that produced from prepared nonautologous products. The use of autologous platelet-rich plasma (platelet gel) and autologous platelet-poor plasma has also been advocated.¹⁷ Some of these methods also rely on exogenous thrombin that may be of human or bovine origin. Thrombin and calcium chloride are combined with the autologous platelet-poor plasma to form fibrin glue. If larger volumes of this plasma are required, it should be possible to return the red blood cells to the patient using autologous blood salvage techniques. If in particular platelets are included, these preparations have some properties of fi-

brin sealants but also contain growth factors that may aid wound healing such as platelet-derived growth factor and transforming growth factor. It has also been suggested that a thinner, less dense layer of fibrin may provide a more physiologic basis for wound healing. However, it appears that these techniques do not include an antifibrinolytic agent such as aprotinin to prevent enzymatic degradation of the sealant.

In the future, techniques may become available that are cost-effective in preparing fibrin sealants by autologous plasma donation that could be carried out in the weeks before surgery to yield large volumes of concentrated fibrin sealants. Similarly, techniques using recombinant DNA technology to produce the components of fibrin sealant would avoid all risks associated with blood-derived products.

There are many potential applications for fibrin sealants in surgery, particularly in aesthetic surgery, where it is especially useful to minimize wound drainage. In our study, we used the total drainage as a marker of postoperative bleeding and serous exudate from the surgical field. Aside from the patient who returned to theater, no other hematomas were noted, suggesting that occult bleeding away from the drains did not influence our results to any measurable extent. In fact, as previously shown, the use of fibrin sealant may obviate the need for surgical drains in face lift surgery.⁴ Beriplast P does not require incubation, making it easy to use, and can be stored out of the refrigerator for 24 hours. It is quick to assemble perioperatively and easy to use with the spray delivery system. Because the fibrin formed by the sealant is identical to naturally occurring fibrin, it is degraded in the same way by fibrinolysis and phagocytosis. As such, Beriplast P mimics natural wound healing.

Although we did not pain score our patients, which in retrospect would have been helpful, fibrin sealant may also be effective in reducing postoperative pain. We feel that the use of fibrin glue is a useful adjunct to face lift surgery to reduce surgical drainage and may obviate the need for drains.¹⁸

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