ORIGINAL ARTICLE

Efficacy of Fibrin Sealant (Human) (Evicel) in Rhinoplasty

A Prospective, Randomized, Single-Blind Trial of the Use of Fibrin Sealant in Lateral Osteotomy

Shepherd G. Pryor, MD; Jonathan Sykes, MD; Travis T. Tollefson, MD

Objectives: To determine whether patients receiving fibrin sealant placed in a single lateral osteotomy site during rhinoplasty will note substantial improvement in pain, bruising, swelling, and overall healing compared with the untreated side and to determine whether blinded observers detect a substantial difference in bruising and swelling on the basis of review of standard postoperative photographs.

Methods: We conducted a prospective, randomized, single-blind, controlled trial of the use of fibrin sealant (human) (Evicel; Johnson & Johnson–Wound Management, Somerville, New Jersey) in 10 consecutive patients undergoing lateral osteotomy in rhinoplasty. Written consent was obtained from all participants. 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. Patients were evaluated on postoperative days 1, 7, and 21 with standard photographic views and a patient questionnaire. The blinded observers consisted of 5 raters familiar with the outcomes and results of rhinoplastic surgery. The observers evaluated all photographs and completed a grading scale to define bruising and swelling on each side.

Results: The mean patient age was 41 years (age range, 21-66 years). Half of the patients were women. The blinded observer Wilcoxon rank sum test revealed a statistically significant difference on postoperative day 1 for bruising ($P<.03$; Wilcoxon critical z value, 1.99) and swelling ($P<.01$; 2.41). Similar findings were discovered on postoperative day 7 for both bruising and swelling ($P<.03$). On postoperative day 21, bruising retained statistical significance ($P<.05$); however, swelling did not achieve statistical significance. Patient questionnaires were evaluated and significance was determined for the treated compared with the untreated side of the nose on postoperative days 1, 7, and 21. Categories included pain, bruising and swelling, and overall rate of healing. The Wilcoxon rank sum test revealed no significance for pain or overall rate of recovery ($P>.06$) on postoperative days 1, 7, or 21. However, bruising and swelling both achieved statistical significance. On postoperative day 1, both pain and swelling scales achieved a significance of $P<.01$ (Wilcoxon critical z value, 2.34). On postoperative day 7, bruising achieved significance at $P<.005$ (Wilcoxon critical z value, 2.63) and swelling achieved significance at $P<.01$ (2.45). Both bruising and swelling achieved equal significance on postoperative day 21 ($P<.01$; Wilcoxon critical z value, 2.57 and 2.45, respectively).

Conclusions: Fibrin sealant applied to a lateral osteotomy site significantly reduced bruising and swelling per patient report on postoperative days 1, 7, and 21. Physician observation reported significant reduction in bruising on postoperative days 1, 7, and 21 and reduction in swelling on postoperative days 1 and 7. The ease of application and versatility of fibrin sealant enable rapid healing after rhinoplasty and produce increased patient satisfaction.

Arch Facial Plast Surg. 2008;10(5):339-344

Author Affiliations: Department of Otolaryngology–Head and Neck Surgery, University of California, Davis Medical Center, Sacramento (Drs Sykes and Tollefson). Dr Pryor is in private practice in Scottsdale, Arizona.

FIBRIN SEALANT HAS BEEN USED for many years and has a wide range of clinical applications for suture support, tissue adhesion, and hemostasis. Fibrin sealant imitates the final phase of the blood coagulation process. Fibrinogen is converted to 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 enabling raw operative surfaces to adhere. The potential advantages of the use of such substances include prevention of hematoma, reduction in surgical time, reduction in flap edema, and shorter recovery time.

The physiologic mechanism that creates fibrin sealant was first described by Morawitz in 1905. In the 1940s, a com-

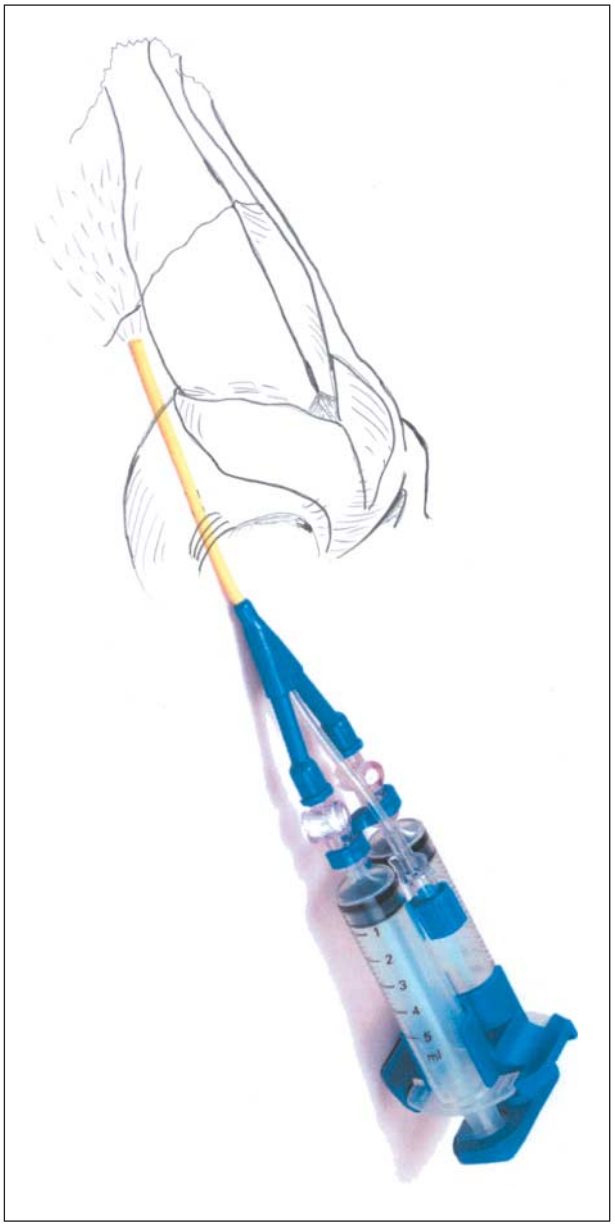

Figure 1. Fibrin sealant (human) (Evicel; Johnson & Johnson–Wound Management, Somerville, New Jersey) applicator device. Approximate location of insertion for application of fibrin glue is along the lateral osteotomy site.

bination of thrombin and fibrinogen from the wound plasma was used in cataract operations.[1] Fibrin glue was originally described in 1970 and is formed by polymerizing fibrinogen with thrombin and calcium.[2] It was originally prepared using donor plasma; however, because of the low concentration of fibrinogen in plasma, the stability and quality of the fibrin glue were low.[3] Commercially pretreated fibrin sealant products were developed to increase the efficacy of forming a stable clot and to provide increased volume of material available. These were shown to be highly efficacious in liver resection and cardiothoracic surgery.[4,5] These products are heat treated, which greatly reduces the risk of disease transmission. The fibrin sealant and delivery system are easy to store and rapid to construct, and, therefore, have enjoyed some use in cosmetic surgery.[6,7]

Fibrin sealant (human) (Evicel; Johnson & Johnson–Wound Management, Somerville, New Jersey) is a plasma cryoprecipitate-based sealant that consists of 2 components: (1) biological active component–2 (BAC2), also called *human clottable protein*, which consists predominantly of fibrinogen and (2) thrombin. BAC2, a concentrated solution of clottable plasma proteins, consists mainly of fibrinogen and other proteins. The thrombin solution contains highly purified human thrombin and calcium chloride for activation of clotting of the final combined product. Thrombin is a highly specific protease that transforms the fibrinogen contained in BAC2 into fibrin.

Rhinoplasty and lateral osteotomy are well suited for the use of fibrin sealant. During lateral osteotomy, the fractured bone and disrupted periosteum are at risk of bleeding that can result in periorbital bruising. As with all surgery, patients desire shorter healing time and lower associated morbidity such as pain, bruising, and bleeding. These need to be minimized in what is both a cosmetic and reconstructive procedure to further control results.

METHODS

The trial was designed as a prospective, randomized, single-blind, controlled trial with approval from the University of California, Davis Institutional Review Board committee. The study material (Evicel) was granted US Food and Drug Administration exemption for use in a human patient population. Ten consecutive patients were asked to participate in the study, all of whom gave informed consent and were recruited into the study. Informed consent involved a discussion with one of the operating surgeons (S.G.P., J.S., and T.T.T.), receipt of a patient's bill of rights, and full disclosure of the study protocol. Exclusion criteria included patients who were pregnant or planned to become pregnant in the near future, patients with a known allergy to blood-related products, and patients medically unstable to undergo surgery. All of the procedures performed were rhinoplasty involving bilateral lateral osteotomy. Patients were unaware of which side was treated with fibrin sealant. No additional cosmetic procedures such as facelift, blepharoplasty, or chin augmentation were performed.

Evicel is provided as a single-use human surgical sealant kit consisting of 2 packages, the first containing 1 vial each of frozen sterile solutions of BAC2 and thrombin and the second containing the sterile application device. It is the only totally human protein–derived, bovine-free fibrin sealant commercially available in the United States. The unit cost for 2 mL of fibrin sealant plus the applicator is $200. The vials are stored in a freezer; when removed and thawed, they are stable for 24 hours. The vials are readily thawed in 5 minutes without the use of a rapid-warming device. After the BAC2 and thrombin solutions are thawed, they are drawn into a unique trilumenal (2 syringe lumens and 1 air lumen for spraying) catheter application device (**Figure 1**). As the plungers are depressed simultaneously, the solutions are mixed by the applicator and sprayed into the operative site. The applicator gently sprays the fibrin sealant into the operative wound as a thin layer and, therefore, allows a relatively small volume (2 mL) of sealant to be delivered evenly. The solutions mix as they exit the catheter during administration, are applied topically by dripping or spraying, and, once applied, are transparent. The reconstituted preparation mimics the final steps in 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.

During rhinoplasty, after lateral osteotomy was completed, a sealed envelope was opened to show randomization to the left or right side. Then 2 mL of fibrin sealant was sprayed into the selected lateral osteotomy site on either the right or the left side. Gentle manual pressure for 3 minutes was applied to both sides of the nose for further hemostasis. Closure of the mucosal incisions to access the osteotomy site was not performed on either side. In each patient, fibrin sealant was delivered to either the right or the left side, with the contralateral side serving as the control. A standard cast dressing was applied externally to the nose in all patients. Standard 2-cm packing was placed bilaterally in all patients overnight.

Patients were seen the next day for removal of packing and assessment. The assessment included postoperative day 1 photographs and a patient questionnaire. The questionnaire was provided and time was allowed for completion without the presence of medical professionals including the primary investigator (S.G.P.). Patients repeated this process on postoperative days 7 and 21. Patients had no knowledge as to which side was treated until the completion of the study.

Standardized background and camera-mounted lighting were used for all photographs, which were obtained using a digital single-lens reflex camera (Nikon D7; Nikon Corp, Tokyo, Japan). In accordance with requirements of the Health Insurance Portability and Accountability Act, all patient data were linked to an alphabetical system to prevent identification and to protect privacy. Photographs were stored on a password-protected computer in a locked room. Only the principal investigator (S.G.P.) and the blinded observers had access to the photographs.

Five raters evaluated each patient's nose and the area on either side of the nose. Each rater was asked to state which side of the nose had less bruising and swelling. The reviewers were blinded as to which side was treated with fibrin sealant. We thought that the treated side was better if at least 4 of the 5 raters agreed. In this case, the treatment was deemed a success or a failure. If the treatment effect was clinically worthwhile, at least 80% of the patients' treated sides were clearly judged better than the untreated sides; that is, treatment of randomly selected patients would have an 80% chance of success. With that assumption and a sample size of 10 patients, we will have 80% power with a 2-sided test of proportion at the $P = .05$ level.[8]

The blinded observers were asked to rate bruising and swelling for each side of the nose on a scale of 0 (0% of the area is bruised and swollen) to 10 (100% of the area is bruised and swollen). When these data were analyzed, these ratings were converted to numbers 0 (best) to 10 (worst), respectively. For each side of the nose, the values from the 5 raters were summed to produce a score in a range from 0 (best) to 50 (worst). The difference score between the treated and untreated sides of the nose was used to quantify the degree to which the treatment helped. Once a difference score for each patient was computed between the treated and untreated sides, a signed rank (Wilcoxon) test of the hypothesis that the median difference is greater than zero was performed.[8]

Each patient was also asked to rate each side of the nose for the percentage of the area treated that had less pain, less bruising, less swelling, and faster overall recovery time on a scale of 0 (0% of the area was bruised or swollen) to 10 (100% of the area was bruised or swollen) (**Figure 2**). When these data were analyzed, these ratings were converted to numbers 0 to 10, respectively. The difference score between the treated and untreated side of the nose was used to quantify the degree to which the treatment helped. To test this hypothesis, a difference score for each patient was computed consisting of the score for the treated side of the nose minus the score for the untreated side. A signed rank (Wilcoxon) test of the hypothesis that the median difference is greater than zero was performed.[8]

Exit Interview

Re: Human Subjects Application, "Efficacy of Evicel in Rhinoplasty (Nose Reshaping)"

Thank you for participating in this study. Please answer the following questions.

1. Please rate the overall recovery period for each side of your rhinoplasty.

	Slow Recovery				Average Recovery					Fast Recovery
R	1	2	3	4	5	6	7	8	9	10
L	1	2	3	4	5	6	7	8	9	10

2. Which side of your rhinoplasty was less painful?

	Minimal Pain				Average Pain					Severe Pain
R	1	2	3	4	5	6	7	8	9	10
L	1	2	3	4	5	6	7	8	9	10

3. Which side of your rhinoplasty had less bruising?

	Minimal Bruising				Average Bruising					Severe Bruising
R	1	2	3	4	5	6	7	8	9	10
L	1	2	3	4	5	6	7	8	9	10

4. Which side of your rhinoplasty has less swelling?

	Minimal Swelling				Average Swelling					Severe Swelling
R	1	2	3	4	5	6	7	8	9	10
L	1	2	3	4	5	6	7	8	9	10

Thank you again for your participation in this study.

Jonathan Sykes, MD, and Shepherd G. Pryor, MD

Figure 2. Patient questionnaire completed on postoperative days 1, 7, and 21.

RESULTS

The mean age of the patients was 41 years (age range, 21-66 years). Half of the patients were women. Eight patients were white, 1 was Hispanic, and 1 was Native American. Six patients received fibrin sealant treatment to the right lateral osteotomy site and 4 patients received treatment to the left lateral osteotomy site.

Five blinded observers rated the patients on the basis of standard facial plastic surgery photographic evidence. Assessments were made of bruising and swelling on each side of the face with no knowledge of which side had been treated. On postoperative day 1, the Wilcoxon rank sum test revealed a statistically significant difference for bruising ($P < .03$; Wilcoxon critical z value, 1.99) and swelling ($P < .01$; 2.41). Similar findings were noted on postoperative day 7 for both bruising and swelling ($P < .03$). On postoperative day 21, bruising retained statistical significance ($P < .05$); however, swelling did not achieve significance.

Patient questionnaires were evaluated and significance was determined for treated vs untreated side of the nose on postoperative days 1, 7, and 21. The Wilcoxon rank sum test revealed no significance for overall rate of recovery or pain ($P > .06$) on postoperative days 1, 7, or

Table. Objective Data Analysis From 5 Blinded Observers

Patient	Xa	Xb	Absolute Xa-Xb	Rank	Wilcoxon Rank Sum Statistic	Calculated Wilcoxon Critical *z* Value	*P* Value
Postoperative day 1							
Bruising							
1	21	41	20	3.5			
2	18	36	14	1.5			
3	8	28	20	3.5			
4	25	45	20	3.5			
5	20	40	20	3.5			
6	10	38	28	9.0	39.5	1.99	<.03
7	25	45	20	3.5			
8	0	43	43	10.0			
9	10	30	20	3.5			
10	0	14	14	1.5			
Swelling							
1	30	30	0				
2	26	26	0				
3	13	34	21	6.5			
4	24	39	15	4.5			
5	22	27	5	1.5			
6	15	30	15	4.5	35	2.41	<.01
7	30	51	21	6.5			
8	14	43	29	7			
9	25	30	5	1.5			
10	0	9	9	3			
Postoperative day 7							
Bruising							
1	26	26	0				
2	15	28	13	1.5			
3	10	25	15	4			
4	20	40	20	6.5			
5	18	36	18	5			
6	10	30	20	6.5	33	1.95	<.05
7	18	31	13	1.5			
8	0	20	20	6.5			
9	14	27	13	1.5			
10	0	0	0				
Swelling							
1	25	25	0				
2	20	20	0				
3	10	27	17	5			
4	25	38	13	4			
5	20	23	3	1			
6	15	15	0		15	1.75	<.05
7	22	32	10	2.5			
8	10	20	10	2.5			
9	20	20	0				
10	0	0	0				
Postoperative day 21							
Bruising							
1	10	25	15	5.5			
2	10	20	10	1.5			
3	5	15	10	1.5			
4	5	5	0				
5	5	15	10	1.5			
6	0	15	15	5.5	17	1.78	<.05
7	10	20	10	1.5			
8	0	0	0				
9	0	0	0				
10	0	0	0				
Swelling							
1	10	10	0				
2	10	15	5	1.5			
3	5	5	0				
4	5	5	0				
5	5	10	5	1.5			
6	0	9	9	4	8.5	1.55	>.05
7	10	10	0				
8	5	10	5	1.5			
9	0	0	0				
10	0	0	0				

Abbreviations: Xa, tabulated scores for the treated side from the 5 blinded observers; Xb, tabulated scores for the nontreated side from the 5 blinded observers.

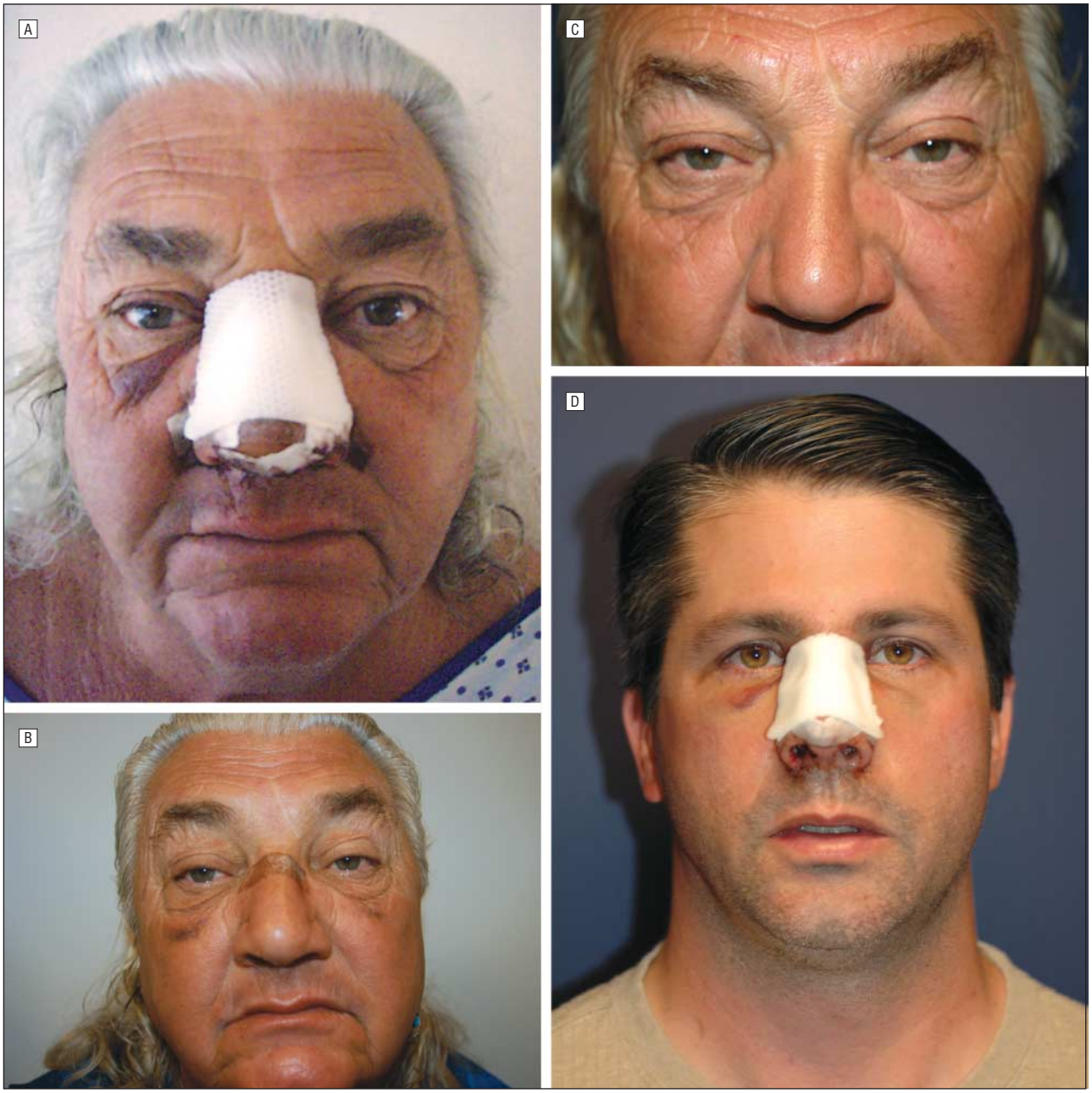

Figure 3. Patient views obtained on postoperative days 1 (A), 7 (B), and 21 (C). D, View of another patient obtained on postoperative day 7 for comparison.

21. However, bruising and swelling both achieved statistical significance. On postoperative day 1, both pain and swelling scales achieved a significance of $P<.01$ (Wilcoxon critical z value, 2.34). On postoperative day 7, bruising achieved significance at $P<.005$ (Wilcoxon critical z value, 2.63) and postoperative swelling achieved significance at $P<.01$ (2.45). Both bruising and swelling achieved equal significance on postoperative day 21 ($P<.01$; Wilcoxon critical z value, 2.57 and 2.45, respectively) (**Table**).

COMMENT

Fibrin sealant can reduce bleeding and is used in almost all specialties, from neurological surgery for dural repair[9] to vascular surgery for intraoperative control of arterial hemorrhage.[10,11] The versatility is such that fibrin glue was used in as many as 5% of all surgical procedures in US hospitals in 1995.[12] Recently, fibrin sealant has obtained some popularity in cosmetic facial plastic surgery for tissue adhesion in craniofacial surgery and endoscopic brow-lifts.[7]

Although the composition and delivery system differ among the commercially available fibrin glue products, we do not believe that the fibrin sealant used in our study differs substantially 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. The 2 notable exceptions to Evicel being the lack of bovine derivatives, which may, in theory, decrease the risk of allergic reaction, and it can be prepared faster than some other options available.

As is the case in any surgical procedure, the use of fibrin sealant is not a replacement for meticulous technique and standard hemostasis. However, in rhinoplasty, especially with the lateral osteotomy technique, the wound bed involves bone and soft tissue and is difficult to access surgically. Fibrin sealant reduces capillary bleeding and serous exudate from the operative surfaces; it does not, however, prevent arterial bleeding.

Risks associated with fibrin sealants include possible transmission of blood-borne diseases. Thrombin, factor XIII, and fibrinogen are isolated from human plasma and, therefore, are associated with the theoretical risk of transmission of hepatitis B and C, human immunodeficiency virus, and human T-cell leukemia or lymphoma virus. One study indicates that transmission of these agents has not occurred in more than 20 000 blood transfusions.[13] Aprotinin, a component of some fibrin sealants, also is associated with the theoretical risk of adverse reaction and transmission of bovine spongiform encephalopathy. However, Evicel is free of this component, thus enhancing its versatility and safety.

Recently, the use of autologous platelet-rich plasma (platelet gel) has been advocated.[14] Autologous whole blood is obtained in the immediate preoperative period and is processed into autologous concentrated platelet-rich plasma using differential centrifugation in a conventional autotransfusion machine. When this platelet-rich plasma is combined with thrombin and calcium chloride, platelet is created. This product is a rich source of growth factors and is effective in accelerating substantial tissue repair and regeneration.[15] A benefit of this gel is that, on activation, platelets release platelet-derived growth factor and transforming growth factor, which are present in high concentrations in platelet gel.[16] Disadvantages include the increase in preparation time because the anesthesiologist must obtain the patients' plasma and approximately 50 to 180 mL of blood must be drawn preoperatively. A centrifuge must be available and, thus, increased preparation time is necessary. This process relies on low patient levels of fibrinogen. In the present study, lateral rhinoplasty osteotomy sites and tissue pockets were small and required small volumes of fibrin sealant for adequate hemostasis, and, therefore, autologous platelet-rich plasma may be cumbersome. Fibrin sealant that is readily available and quickly prepared enables the surgeon versatility in time management and patient care.

This study indicates that fibrin glue can temporarily reduce the morbidity associated with rhinoplasty after lateral osteotomy, with decreased ecchymoses and swelling. The immediate postoperative bruising and swelling associated with osteotomy is significantly reduced with immediate intraoperative placement of a small volume of fibrin sealant. Both patients and physicians noted substantial improvement in both bruising and swelling until postoperative day 7 and substantial improvement in bruising through postoperative day 21 (**Figure 3**). Postoperative recovery using Evicel enables patients to return to work and day-to-day activities sooner. A rapid-healing rhinoplasty is a favorable option in many patients. Fibrin glue has been underused in the past because of concerns about disease transmission or allergic reaction to bovine components. Likewise, increased preparation time and rewarming devices made some commercially available sealants cumbersome and difficult to adequately use effectively. Evicel lacks both of these disadvantages.

Accepted for Publication: March 7, 2008.
Correspondence: Shepherd G. Pryor, MD, Valley Facial Plastic Surgery, 8752 E Via de Commercio, Scottsdale, AZ 85258 (sheppryor@yahoo.com).
Author Contributions: Dr Pryor had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Pryor and Sykes. *Acquisition of data:* Pryor and Tollefson . *Analysis and interpretation of data:* Pryor and Sykes. *Drafting of the manuscript:* Pryor. *Critical revision of the manuscript for important intellectual content:* Pryor, Sykes, and Tollefson. *Statistical analysis:* Pryor. *Administrative, technical, and material support:* Pryor. *Study supervision:* Sykes and Tollefson.
Financial Disclosure: None reported.
Role of the Sponsor: Johnson & Johnson–Wound Management had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Additional Contributions: Evicel and applicator devices were provided by an investigator-initiated grant from Johnson & Johnson–Wound Management.

REFERENCES

1. Gareis-Helferich E, de Decker W, Gross G, Dokter P, Geering H. Closure of the conjunctiva using fibrinous tissue adhesives [in German]. *Klin Monatsbl Augenheilkd*. 1968;153(1):74-78.
2. Matras H. Effect of various fibrin preparations on reimplantation in the rat skin [in German]. *Osterr Z Stomatol*. 1970;67(9):338-359.
3. Gibble JW, Ness PM. Fibrin glue: the perfect operative sealant? *Transfusion*. 1990; 30(8):741-747.
4. Noun R, Elias D, Balladur P, et al. Fibrin glue effectiveness and tolerance after elective liver resection: a randomized trial. *Hepatogastroenterology*. 1996;43 (7):221-224.
5. Rousou J, Levitsky S, Gonzalez-Lavin L, et al. Randomized clinical trail of fibrin sealant in patients undergoing resternotomy or reoperation after cardiac operations. *J Thorac Cardiovasc Surg*. 1989;97(2):194-203.
6. Marchac D, Sándor G. Face lifts and sprayed fibrin glue: an outcome analysis of 200 patients. *Br J Plast Surg*. 1994;47(5):306-309.
7. Marchac D, Renier D. Fibrin glue in craniofacial surgery. *J Craniofac Surg*. 1990; 1(1):32-34.
8. Van Belle G, Fisher LD, Heagerty PJ, Lumley T. *Biostatistics: A Methodology for the Health Sciences*. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc; 2004.
9. Cosgrove GR, Delashaw JB, Grotenhuis JA, et al. Safety and efficacy of a novel polyethylene glycol hydrogel sealant for watertight dural repair. *J Neurosurg*. 2007; 106(1):52-58.
10. L'Esperance JO, Sung JC, Marguet CG, et al. Controlled survival study of the effects of Tisseel or a combination of FloSeal and Tisseel on major vascular injury and major collecting-system injury during partial nephrectomy in a porcine model. *J Endourol*. 2005;19(9):1114-1121.
11. Reuthebuch O, Lachat ML, Vogt P, Schurr U, Turina M. FloSeal: a new hemostatic agent in peripheral vascular surgery. *Vasa*. 2000;29(3):204-206.
12. Spotnitz WD. Fibrin sealant in the US: clinical use at the University of Virginia. *Thromb Haemost*. 1995;74(1):482-485.
13. Regan FA, Hewitt P, Barbara JAJ, Contreras M. Prospective investigation of transfusion transmitted infection in recipients of over 20,000 units of blood [published correction appears in *BMJ*. 2000;29(321):266]. *BMJ*. 2000;320(7232):403-406.
14. Kjaergard HK, Trumbull HR. Vivostat system autologous fibrin sealant: preliminary study in elective coronary bypass grafting. *Ann Thorac Surg*. 1998;66 (2):482-486.
15. Hood AG, Hill AG, Reeder GD, et al. Perioperative autologous sequestration, III: a new physiologic glue with wound healing properties. *Am Acad Cardiovasc Perfusion*. 1993;14:126.
16. Martin P, Hopkinson-Woolley J, McCluskey J. Growth factors and cutaneous wound repair. *Prog Growth Factor Res*. 1992;4(1):25-44.