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Randomized clinical trial of fibrin sealant in patients undergoing resternotomy or reoperation after cardiac operations

A multicenter study

A multicenter study was conducted to test the efficacy and safety of fibrin sealant as a topical hemostatic agent in patients undergoing either reoperative cardiac surgery (redo) or emergency resternotomy. A total of 333 patients from 11 centers in the United States were included in the study. Patients were randomly assigned to initially receive the fibrin sealant or a conventional topical hemostatic agent when such was required during an operation. The end point used to evaluate the agent's efficacy was local hemostasis, the number of bleeding episodes controlled within 5 minutes. The fibrin sealant group from the prospective study was compared with historical matched control subjects for postoperative blood loss, need for resternotomy, blood products received, and hospital stay. It was also compared with historical nonmatched control subjects for the incidence of resternotomy and mortality. The results showed a 92.6% success rate for fibrin sealant in controlling bleeding within 5 minutes of application, compared with only a 12.4% success rate with conventional topical agents ($p < 0.001$). Fibrin sealant also rapidly controlled 82.0% of those bleeding episodes not initially controlled by conventional agents. High-volume postoperative blood loss was significantly less ($p < 0.05$) in the fibrin sealant group than in the matched controls. Additionally, resternotomy rates after redo operations were significantly lower in the fibrin sealant group (5.6%) than in the nonmatched historical control group (10%) ($p < 0.0089$). There were no significant differences in hospital stay or blood products received between the fibrin sealant group and matched historical controls and no difference in mortality between the fibrin sealant group and nonmatched historical controls. There were no documented instances of adverse reactions, transmission of viral infection (hepatitis B, non-A/non-B hepatitis), or human immunodeficiency virus seroconversion. This study shows that fibrin sealant is safe and highly effective in controlling localized bleeding in cardiac operations. Fibrin sealant reduces postoperative blood loss and decreases the incidence of emergency resternotomy. These findings make fibrin sealant a valuable hemostatic agent in cardiac surgery.

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The use of fibrin sealant* in cardiovascular surgery was pioneered by Borst[1] in Hannover, Germany; it has been used in cardiovascular surgery and other surgical specialties in Europe for some 10 years. Borst's experience, as well as substantial clinical and experimental literature on the subject, suggests that the use of fibrin

*Tisseel, produced by Immuno AG, Vienna, Austria.

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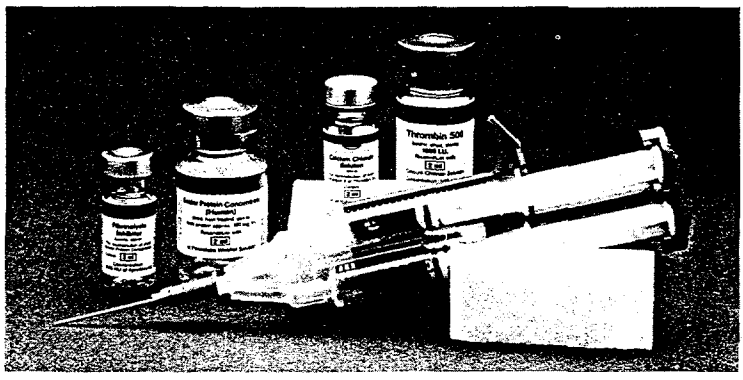

Fig. 1. Fibrin sealant kit. This includes the sealer protein concentrate, aprotinin, a fibrinolysis inhibitor, thrombin 500, and calcium chloride solution. Also shown is the Duploject syringe after assembly and the Helistat carrier.

sealant results in local hemostasis and consequently reduces blood loss, operative time, the need for resternotomy, and overall mortality.[1-4] Fibrin sealant at the present time is not approved for general use in the United States. In early 1986, Food and Drug Administration approval for clinical investigation was obtained and a multicenter study was initiated to study the efficacy and safety of fibrin sealant as a topical hemostatic agent in patients having repeat cardiac operations ("redo" patients) and in patients requiring emergency resternotomy for postoperative bleeding.

Materials and methods

Components. Fibrin sealant* components are supplied in a kit (Fig. 1) that contains the following:

1. Sealer protein concentrate (human), *heat treated,* dried, sterile, total protein approximately 130 mg/ml; obtained from plasma that is routinely tested for hepatitis B surface antigen (HBsAg), anti-human immunodeficiency virus (anti-HIV) antibody, and alanine aminotransferase (ALT)
2. Fibrinolysis inhibitor (aprotinin), concentration: 3000 KIU/ml
3. Thrombin 500, bovine, dried, concentration: 500 IU/ml
4. Calcium chloride solution, 40 mmol/L

The substances in the kit provide two final components after reconstitution: the sealer solution and the thrombin solution. To obtain the sealer solution, sealer protein concentrate is dissolved in the accompanying solution of fibrinolysis inhibitor. The sealer solution is drawn into a 1 ml syringe and must be used within 4 hours. Dried thrombin is dissolved in calcium chloride solution to yield the thrombin solution, drawn in a separate 1 ml syringe. Preparation of the solutions, requiring dissolving and mixing the dried agents, takes 10 minutes. The two 1 ml syringes may be mounted on a Y-connector to which an interchangeable blunt needle is attached to form the Duploject* device (Fig. 1).

*Immuno AG, Vienna, Austria.

For the control of bleeding, the sealant is sometimes applied with a suitable carrier. In Europe, collagen felt, fleece, or foam of collagen has been widely used. In this study, Helistat* has been used uniformly in all centers as the carrier material. This is a collagen pledget (Fig. 1) that is absorbed in the course of normal wound healing.

Conventional topical hemostatic agents used as controls in the institutions participating in the study include Avitene,† Gelfoam,‡ Oxycel,§ Surgicel,‖ and Thrombinar.¶

Application methods. Two methods were used in this study for the application of fibrin sealant at the bleeding site. The first consisted of applying the sealer solution onto the carrier (in this case the Helistat carrier) directly from the syringe. A few drops of the thrombin solution were then sprinkled from the second syringe onto the side of the Helistat holding the sealer solution and the Helistat carrier was then quickly pressed onto the bleeding site for approximately 60 seconds, either by a gloved, clean index finger or by a clean surgical instrument such as the handle of a forceps. The surgeon's finger or the instrument was then taken off carefully from the carrier in order to avoid loosening it from the tissue. After the gluing, the carrier was not removed from the bleeding site.

The second method of application used the Duploject device (Fig. 1). The sealer and thrombin solutions travel through the Y-connector separately until they meet and mix within the needle. The coagulum takes several seconds to form after the sealant mixes with the thrombin solution. Thus the fibrin coagulum forms only after it is applied to the bleeding surface. If reapplication from the same syringe is required, the needle is changed, since the fibrin coagulum within it usually obstructs flow. The Helistat carrier, if so chosen by the surgeon, was immediately placed over the forming fibrin coagulum on the bleeding surface and gentle pressure was applied for 60 seconds. Otherwise, the sealant was left to form a coagulum at

*United States Surgical Corporation, Norwalk, Conn.

†Avicon, Inc., Humacao, Puerto Rico.

‡Johnson and Johnson Products, Inc., New Brunswick, N.J.

§Deseret, Sandy, Utah.

‖Upjohn Company, Needham Heights, Mass.

¶Armour Pharmaceuticals, Tarrytown, N.Y.

Fig. 2. Fibrin sealant coagulum on the anterior surface of the right ventricle.

the bleeding site without the use of Helistat or any other material (Fig. 2).

Conventional topical hemostatic agents were applied to the bleeding site directly with temporary pressure similar to the method used with Helistat and fibrin sealant.

Protocol

Patient entry criteria. Only redo and resternotomy patients were eligible for entry into the multicenter study. A redo operation was defined as any cardiac operation involving cardiopulmonary bypass in a patient who had a previous cardiac operation. Resternotomy was defined as the reopening of the sternum to control bleeding within 24 hours of an earlier cardiac procedure. Patients of both sexes were eligible and there were no age limits. Informed consent was required for each patient. Resternotomy patients may not have been awake between the two interventions. For that reason, informed consent was requested before the initial operation from all patients who were identified by the investigator as being eligible and who were to undergo primary cardiac operations or redo operations. Patients with severe renal or hepatic disease with an attendant increased risk of bleeding and those with congenital or acquired bleeding diathesis were excluded by the protocol. Although not an entrance requirement, it was recommended that patients be taken off platelet inhibitors 72 hours before the operation. Specific antiplatelet agents used and the date each was discontinued were recorded.

Group assignment in prospective study. Patients with persistent localized bleeding after protamine administration and after surgical hemostatic methods had been used and proved ineffective, or were deemed impractical, were randomly assigned to group A or B (Fig. 3). Group A patients received fibrin sealant first; group B patients received conventional topical agents first. The choice of conventional topical agent to be used was left to the discretion of the surgeon. Patients were assigned to either group A or B by a computer-generated randomization list. The randomization scheme for the study was stratified by clinic and used balanced blocks of four. These agents were given a full 5 minutes to work. If they were ineffective after 5 minutes, the surgeon had the option of switching to the alternate hemostatic therapy. The type of hemostatic therapy used and the time of application, as well as the time in which the bleeding stopped, were recorded.

As noted on the protocol in Fig. 3, fibrin sealant could be used in group B patients whose bleeding did not stop within 5 minutes of application of conventional agents. Conversely, conventional agents could be used if fibrin sealant failed. The success rate in controlling bleeding in this group of patients with fibrin sealant or conventional agents as a second alternative was recorded. As a result, group B could potentially benefit from the hemostatic effectiveness of fibrin sealant, and differences in blood loss, transfusion requirements, resternotomy, and mortality rates between groups might thereby be reduced. For that reason, all group A and group B patients who received fibrin sealant were pooled and comparisons were made to historical matched and nonmatched controls for these secondary end points.

Bleeding episodes were excluded from analysis for the three reasons: (1) violation of group assignment (wrong treatment first); (2) less than 5 minutes allowed to see if treatment failed before an alternate therapy was begun; and (3) clinical information needed to determine treatment success or failure was missing from the completed forms.

Historical control group comparisons. In addition to the

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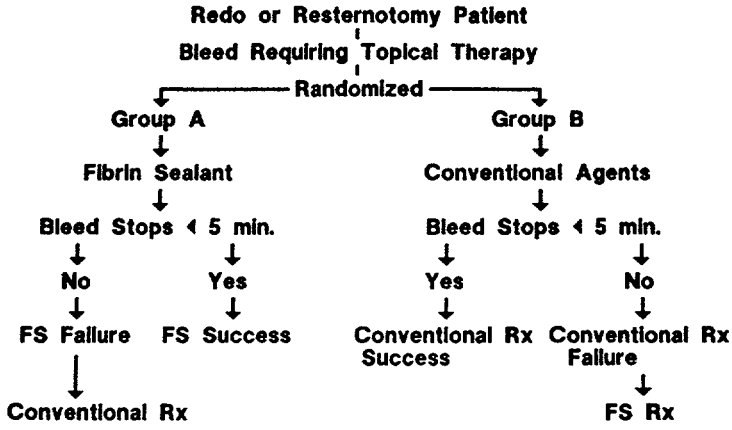

Fig. 3. Protocol for randomized prospective study of topical hemostatic efficacy of fibrin sealant versus conventional topical agents.

Table I. *Patient distribution by center and group assignment*

	Groups					
	A		*B*		*A and B*	
Center	*No.*	*%*	*No.*	*%*	*No.*	*%*
1. Baystate Medical Center	10	6.1	12	7.1	22	6.6
2. Henry Ford Hospital	16	9.8	16	9.5	32	9.6
3. Abbott Northwestern Hospital	7	4.3	7	4.1	14	4.2
4. Deborah Heart and Lung Center	12	7.3	12	7.1	24	7.2
5. Maine Medical Center	7	4.3	10	5.9	17	5.1
6. The Sanger Clinic	20	12.2	19	11.3	39	11.7
7. University of California	2	1.2	1	0.6	3	0.9
8. University of Illinois	5	3.0	7	4.1	12	3.6
9. Washington University	9	5.5	12	7.1	21	6.3
10. Buffalo General Hospital	1	0.6	4	2.4	5	1.5
11. Cleveland Clinic Foundation	75	45.7	69	40.8	144	43.3
Total (11 centers)	164	100.0	169	100.0	333	100.0

concurrent control group of patients used to assess the efficacy of hemostasis during surgery, three other historical groups of patients were compared with patients receiving fibrin sealant (from both group A and group B) for secondary end-points. The first group consisted of matched historical controls operated on during the 2 preceding years in the same center matched by age, primary operation (coronary artery bypass [CABG], valve, other) and type of operation (redo or emergency resternotomy). In the matched pair analysis, differences in blood drainage, blood requirements, hospital stay, and resternotomy rates were compared between patients receiving fibrin sealant and their matched controls. Matched pair analysis was performed in 10 of the 11 participating centers. The number of matched pairs varied with each secondary end point considered. The number of pairs ranged from 56 (for postoperative drainage volumes) to 88 (for the incidence of resternotomy).

The other two control groups consisted of nonmatched historical patients from the same centers. One group consisted of 300 nonmatched redo patients of all types operated on in the preceding 1 year in 10 of the 11 participating centers. This group was compared to 159 group A patients as well as group B redo patients who received fibrin sealant in the concurrent study. Two end points were examined—incidence of resternotomy and mortality. The last group of unmatched historical controls consisted of 149 redo CABGs performed during the preceding 6 months in one center only (center 11). This group was compared to 74 fibrin sealant patients from both groups A and B of the concurrent study who underwent redo CABG only. Again, two secondary end points were examined—the incidence of resternotomy and mortality.

Fibrin sealant safety studies. All patients in the prospective study were observed for reactions to fibrin sealant or conventional agents intraoperatively or postoperatively. Patients were also observed for viral transmitted diseases such as hepatitis or HIV infections. Additionally, serial serologic studies were conducted in a subgroup of the prospective population of one center, No. 11. Blood samples for hepatitis

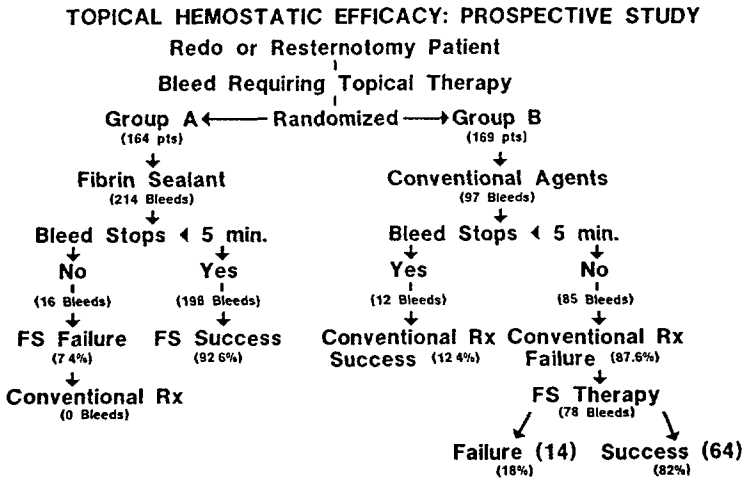

Fig. 4. Summary of results of randomized prospective study of fibrin sealant versus conventional agents for topical hemostasis.

Table II. *Demographic characteristics of fibrin sealant patients (group A, 49.2%) and concurrent controls (group B, 50.8%)*

	Group A (n = 164)		*Group B (n = 169)*		
Characteristics	*No.*	*%*	*No.*	*%*	*p Value*
Male sex	126	76.8	117	69.2	NS
Age (mean yr)	56		57		NS
Cardiac disease, primary diagnosis CAD	118	72.0	105	61.3	NS
Type of operation					
Redo	149	90.9	154	91.1	NS
Resternotomy	15	9.1	15	8.9	NS
Preop. anticoagulation					
Anticoagulants	27		22		NS
Antiplatelets	48		45		NS
Both	5		9		NS

CAD, Coronary artery disease.

B, non-A/non-B hepatitis, and HIV antibody were drawn preoperatively (sample 0), at 2 to 3 weeks (sample 1), 6 to 8 weeks (sample 2), 2 to 4 months (sample 3), and 6 months (sample 4). Sixty-three patients were entered into this study.

Statistical analysis. To identify an increase in the proportion of bleeding episodes controlled with fibrin sealant from 0.50 to 0.70 at $p = 0.05$ and power = 0.90, we calculated before the prospective study that a sample size of 100 patients in each group would be needed. Statistical analysis was conducted with the Statistical Package for the Social Sciences/Personal Computer (SPSS, Inc., Chicago, Ill.). Data were grouped by treatment assigned in the randomized clinical trial unless otherwise specified. Paired analysis of dichotomous (Fleiss,[5] 1973) or continuous data was used for the matched pairs study.

The study was closed on Jan. 20, 1987, after forms had been received on 333 analyzable patients. They comprised 189 patients undergoing redo or resternotomy from 10 centers and 144 patients undergoing only redo cardiac procedures from a single center, No. 11.

Results

Data from 333 operations in 333 patients were analyzed. The number of analyzable patients varied slightly by end point. Where relevant, these differences are discussed separately for the specific end point. Table I shows the participating centers and the number of patients contributed by each center. Table II shows the demographic characteristics of the fibrin sealant and concurrent control groups (group A versus group B). One hundred sixty-four patients (49.2%) were included as group A, or fibrin sealant patients; 169 patients

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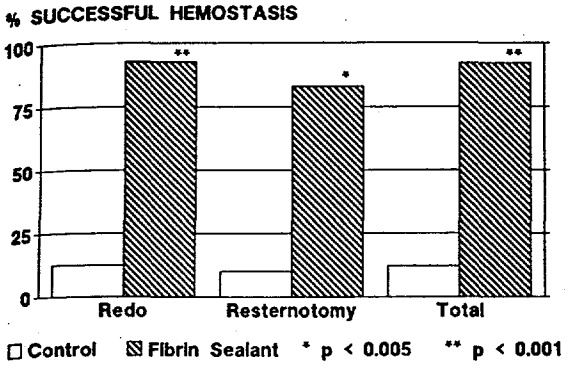

Fig. 5. Hemostatic success of fibrin sealant versus conventional agents by type of operation, i.e., redos versus resternotomies.

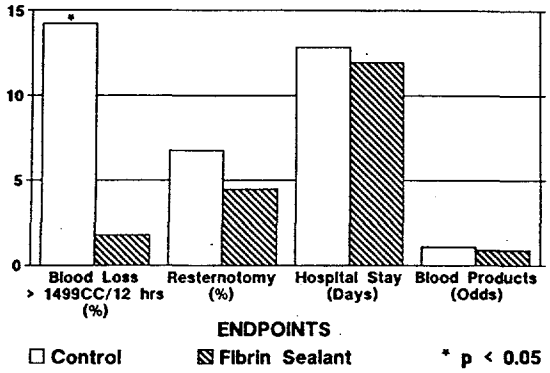

Fig. 6. Comparison of secondary end points between fibrin sealant patients (group A and group B) and historical matched control patients.

(50.8%) were included as group B, or control patients receiving conventional topical agents. The fibrin sealant and conventional topical agent control groups were comparable in sex ratios, age, cardiac disesae (the percent of total with primary diagnosis being coronary artery disease), the type of operation (the percent of the operations entered that were redos versus those that were emergency resternotomies), and the administration of preoperative anticoagulants and/or antiplatelet agents.

Concurrent group analysis—hemostatic efficacy. A total of 473 bleeding episodes were reported in 333 patients. Of these, 311 qualified for analysis. In group A patients, 214 bleeding episodes were included for analysis and 38 were excluded for the reasons previously outlined. In group B, 97 bleeding episodes were included for analysis and 124 were excluded. Of the 311 analyzable bleeding episodes, 289 or 92.9% were in redo operations and 22 or 7.1% were in emergency resternotomy operations. Fig. 4 shows a summary of results in the prospective study. One hundred ninety-eight (92.6%) of the 214 included bleeding episodes treated with fibrin sealant were controlled within 5 minutes. By contrast, only 12 (12.4%) of the 97 episodes treated with conventional topical agents were controlled within 5 minutes. The difference in the proportion of bleeding episodes that stopped within 5 minutes between the two groups is highly significant ($p < 0.001$). Fibrin sealant was superior to conventional agents in each operative setting, both redo operations (93.1% versus 12.6% success) and emergency resternotomies (83.3% versus 10% success) (Fig. 5). There was no significant difference between the success of fibrin sealant to control bleeding in redo versus resternotomy operations. Additionally, fibrin sealant successfully controlled bleeding in other surgical subgroups such as redo operations for coronary artery disease (93% success for fibrin sealant versus 12% success for conventional topical agents, $p < 0.001$); and for noncoronary cardiac disease (92% for fibrin sealant versus 13% success for conventional topical agents, $p < 0.001$). The effectiveness of fibrin sealant and the unsatisfactory results obtained with conventional topical agents were also demonstrated within each center that contributed more than eight bleeding episodes. Success rate for fibrin sealant ranged from 58% to 100%, whereas that of conventional topical agents ranged only from 3% to 38% in the 11 centers. Except for one center that contributed only eight bleeding episodes (seven fibrin sealant, one conventional topical agents), the p value comparing the success rate of fibrin sealant versus the conventional topical agents was less than 0.05 ($p < 0.001$ in six of the 11 centers).

According to the protocol, if fibrin sealant or conventional agents failed to control bleeding after 5 full minutes of observation, the alternate agent could be used. Of 97 included group B bleeding episodes, conventional agents failed in 85 (87.6% failure rate). Fibrin sealant was subsequently used in 78 of these. In 64 of the 78 episodes (82.0%), fibrin sealant stopped the bleeding within the next 5 minutes even though the patients had bled for at least 5 minutes before fibrin sealant use. It should also be mentioned that of 71 group B exclusions in which the surgeon first used fibrin sealant instead of a conventional agent called for by randomization, 68 episodes were analyzable. Bleeding stopped in less than 5 minutes in 67 of 68 such bleeding episodes (a failure rate of only 1.4%).

In 16 included bleeding episodes, fibrin sealant did not stop the bleeding within 5 minutes. Although surgeons had the option to use conventional agents, these

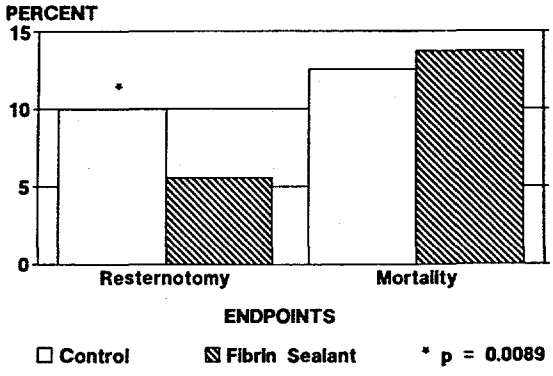

Fig. 7. Comparison of the incidence of resternotomy and mortality between the fibrin sealant group of redo patients and historical nonmatched redo patients in 10 of 11 centers.

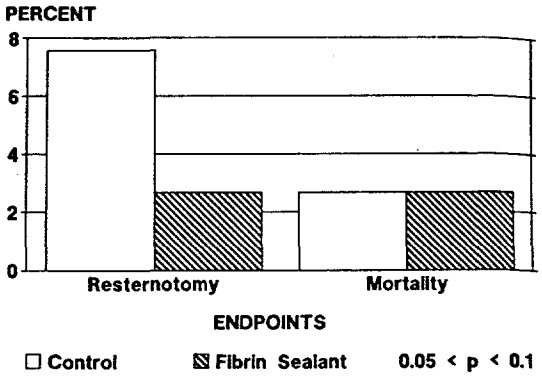

Fig. 8. Comparison of the incidence of resternotomy and mortality between fibrin sealant redo CABG patients and nonmatched historical redo CABG patients in one center only (No. 11).

were not used in this group. Five of the 16 fibrin sealant failures in group A came from one center. In that center, five of 12 group A bleeding episodes failed to stop in 5 minutes (41% failure rate). Thus, overall, 31.3% (five of 16 failures) occurred at a single center, which contributed 5.6% of group A bleeding episodes. This could suggest that there might have been a technical problem in the use of fibrin sealant in that particular center. When results from this center are excluded, the group A failure rate declines from 7.4% to 5.4%.

A single center (No. 11) specifically permitted applications of fibrin sealant before protamine administration. Forty-one such bleeding episodes were identified. One of the 41 episodes was controlled within 6 minutes and another one within 5 minutes. In all other remaining episodes (39), bleeding stopped within 2 minutes, even though the patients were still heparinized.

In a group of 107 patients, the Duploject device was used to apply fibrin sealant. Eighty-seven bleeding episodes were identified in which the Duploject syringe alone was exclusively used to apply the fibrin sealant without the use of a carrier. Of these, 82 were controlled within 5 minutes (94.3% success rate).

Fibrin sealant group versus historical matched controls. Hemostatic efficacy of fibrin sealant was evaluated by examining indirect criteria for successful hemostasis in matched pairs from 10 of the 11 centers. The results of this analysis are shown in Fig. 6.

Since successful sealing of intraoperative bleeding sites should reduce intrathoracic blood loss, cumulative drainage volumes were examined at 12, 24, and 48 hours postoperatively. The 12-hour volumes were considered especially critical, since this initial fluid contains more blood than later drainage. Eighty-eight matched pairs were identified in which the 12-hour cumulative drainage was accurately recorded. The total 12-hour average drainage for the fibrin sealant group was 740 ml, whereas that of the matched controls was 819 ml. The difference between the two was not significant ($p = 0.348$). The possibility that the proportion of patients with high initial blood loss might differ between the groups was then examined. Patients and control subjects were classified according to whether their blood loss was higher or lower than the predetermined cutoff level. These data were analyzed as matched pairs with dichotomous outcomes.[5] The cutoff point of 1499 ml was proposed a priori for the data (when available) based on the distribution of drainage volumes reported by Salzman and colleagues[6] for a similar group of patients. Of 56 matched pairs in whom these 12-hour cutoff points were available, eight patients (14.3%) from the control group had more than 1499 ml of blood within the first 12 hours, whereas in the fibrin sealant group only one (1.8%) patient had more than this volume. The difference was significant ($p < 0.05$). Expressed otherwise, patients in the control group were eight times more likely to bleed in excess of 1499 ml within the first 12 hours as compared with the fibrin sealant group.

Resternotomy rates were used as an indirect method to determine the efficacy of fibrin sealant in surgical hemostasis. Comparing the fibrin sealant group of redo patients with a matched historical group of redo patients, there were four resternotomies for bleeding in the fibrin sealant group (4.5%) versus six resternotomies in the control group (6.8%), with 88 matched pairs analyzed. This difference was not statistically significant.

Hospital stay in 70 matched pairs did not differ significantly between the patients treated with fibrin sealant and their matched controls (12 versus 12.9

Table III. *Fibrin sealant (FS) safety—viral serologic studies*

	Hepatitis B		*Non-A/non-B*		*HIV*	
	FS	*Control*	*FS*	*Control*	*FS*	*Control*
No. tested	24	11	20	13	26	12
Passive transfer	1*	0	1*	0	0	0
Negative	23	11	19	13	26	12

*Same patient received *massive* blood and blood product transfusions

days). Blood products received were also evaluated in 86 matched pairs as an indirect means to assess fibrin sealant efficacy. The blood products examined were whole blood, packed cells, autotransfusion, platelet concentrates, cryoprecipitate, fresh frozen plasma, and albumin. Analysis classified subjects as having received no blood products (or albumin only) versus any other blood product. This was referred to as the "none versus any" comparison. This analysis failed to demonstrate a decrease in blood product usage in association with fibrin sealant in 10 centers. The odds ratio for no blood usage was 0.9 for the fibrin sealant series patients versus 1.1 for the matched control group.

Fibrin sealant group versus historical nonmatched controls

All redo patients—10 centers. Ten of 11 centers compared group A and B redo patients who received fibrin sealant in the prospective study (159 patients) with *all* redo patients operated on during 1985 (300 patients). End points evaluated were the incidence of resternotomy and mortality (Fig. 7). Mortality was not different in the two groups; this is a crude criterion since it is affected by many other factors. Incidence of resternotomy, however, was significantly lower in the fibrin sealant group (5.6%) than in the nonmatched control group (10.0%), $p = 0.0089$.

Redo CABG operations only—center 11. In center 11, redo CABG patients who received fibrin sealant in groups A and B (74 patients) were compared to historical nonmatched redo CABG patients operated on within 6 months preceding the prospective study (149 patients). End points studied were incidence of resternotomy and mortality (Fig. 8). Mortality was identical in between the two groups. Although resternotomy was more frequent in the historical control group (7.4 versus 2.7%), this difference was not statistically significant ($p < 0.1$).

Fibrin sealant safety

Clinical observations. All patients were observed for any adverse reactions during or after the administration of fibrin sealant and/or conventional topical agents. No adverse reactions were reported in either group.

Serologic studies. Viral serologic studies were conducted as part of a safety evaluation of fibrin sealant in one center (No. 11) (Table III). A total of 63 patients were entered into the study. Thirty-seven patients were tested for hepatitis B, (25 fibrin sealant, 12 control), 33 patients (20 fibrin sealant, 13 control) for non-A/non-B hepatitis, and 38 patients (26 fibrin sealant, 12 control) for HIV seroconversion. No patient had hepatitis B, non-A/non B hepatitis, or HIV antibody. With regard to hepatitis B, anti-hepatitis B surface antibody was detectable in three patients. In two patients (one in the fibrin sealant group and one in the conventional group) anti-hepatitis B surface antibody and anti-hepatitis B core antibody, were both present in sample 0 (pretreatment). Therefore, the number of patients eligible for hepatitis B evaluation was reduced from 37 to 35 (24 fibrin sealant and 11 control).

In the third patient in whom anti-hepatitis B surface antibody appeared after fibrin sealant, preoperative sample 0 was negative for anti-hepatitis B surface antibody and anti-hepatitis B core antibody, and samples remained negative for anti-hepatitis B core antibody throughout the observation period. The anti-hepatitis B surface antibody titer was very high on the first postoperative sample (603 mU/ml), declined markedly thereafter (sample 2: 226 mU/ml; sample 3: 19 mU/ml), and had completely disappeared at 6 months. This strongly suggests passive transfer. In fact, this patient had received 103 units of banked blood products intraoperatively and postoperatively. These included packed cells, platelets, fresh frozen plasma, and cryoprecipitate.

For non-A/non-B hepatitis, only one of 33 patients (same patient with massive transfusions and passive transfer of anti-hepatitis B surface antibody) had alanine aminotransferase levels greater than 2.5 times the upper limit of normal; these returned to normal levels 6 months postoperatively. HIV seroconversion did not occur in any of the 38 patients (26 fibrin sealant and 12 control patients) with adequate samples (6 months after the operation).

Discussion

Bleeding can occur during or after cardiovascular operations and may sometimes require postoperative

emergency resternotomy for effective control. Such bleeding may be the result of a coagulopathy, inadequate reversal of heparin, surgical technique, poor tissue characteristics, and inaccessibility of bleeding sites to "surgical" control. Sometimes repeated surgical attempts (i.e., suture, cautery) to control such bleeding may fail or may be impractical because of the particular site of bleeding or character of the tissues. The need to control this type of bleeding in the past stimulated the development of synthetic glues.[7,8] Synthetic glues, however, required dry surfaces to bring about hemostasis and sometimes resulted in severe inflammatory reactions. Hence they never gained popularity as topical hemostatic agents in surgery. Fibrin sealant was first used in cardiovascular surgery by Spangler[9] in 1976 and was subsequently reported by other European investigators in aortic dissection[10] and the sealing of vascular grafts.[11] Since then there has been an abundance of literature, mainly from European centers, commending its clinical effectiveness in cardiac and other operations.[1,12-14]

Formation of fibrin from fibrinogen and its cross-linkage by activated factor XIII represents the end stage of the coagulation scheme. Fibrinogen conversion into fibrin monomers is mediated by thrombin, which is produced from prothrombin. Fibrin monomers combine to form fibrin polymers which, in the presence of factor XIII and calcium, are converted to insoluble fibrin. In the living organism fibrin is continuously undergoing fibrinolysis. To prevent fibrinolysis from occurring prematurely and jeopardizing hemostasis, an antifibrinolytic agent is necessary; in the case of fibrin sealant, aprotinin has been incorporated. The resulting coagulum adheres well to tissue, which explains the hemostatic effect seen in this and other studies.

The efficacy of fibrin sealant has been clearly demonstrated in the concurrent study. The difference in success rate between fibrin sealant and conventional topical hemostatic agents was highly significant (92.6% versus 12.4%, $p < 0.001$). In 10 of the 11 participating centers the protocol specified that fibrin sealant should be applied after heparin reversal by protamine. In center 11, however, the protocol allowed application of fibrin sealant to bleeding sites while the patient was still fully heparinized. In this setting, fibrin sealant was also shown to be highly successful in achieving hemostasis (40 of 41 studied bleeding episodes were controlled within 5 minutes). The protocol allowed use of fibrin sealant in a number of patients in whom conventional topical agents had failed to control localized bleeding. Here again its efficacy was proved, with a success rate of 82.0%. Applied directly with the Duploject device (without the use of the carrier Helistat), fibrin sealant was equally effective (94.3% success). Thus fibrin sealant achieved local hemostasis in a variety of settings and methods of application.

In addition to the concurrent study, the fibrin sealant group was compared with matched and unmatched historical control patients. There was indirect evidence of the efficacy of fibrin sealant in hemostasis by a reduction of resternotomy rates and the rate of postoperative bleeding in the fibrin sealant group. Bleeding in the first 12 postoperative hours is especially significant since most of the chest drainage is blood in contrast to drainage after that period when the drainage might become more serosanguineous than pure blood. The end point in control of operative bleeding is to shorten the operation, prevent complications from continued hemorrhage, and minimize reoperations.

Donors of plasma for the collection of sealer protein concentrate are tested for hepatitis B surface antigen, anti-HIV antibody, and alanine aminotransferase levels. Donors with hepatitis B surface antigen, anti-HIV antibody, or elevated alanine aminotransferase levels are excluded from the plasmapheresis program. In addition, sealer protein concentrate is subjected to a product-specific heat treatment. This treatment has been shown to inactivate the HIV virus, as well as a panel of model viruses. The safety of fibrin sealant has been tested over a decade in thousands of cases in European centers.[15] Serologic studies were performed in this study to detect markers for hepatitis B, non-A/non-B hepatitis, and/or HIV. During the course of the concurrent study, no patient exhibited either hepatitis B or non-A/non-B hepatitis. In 38 patients studied with serial serologic tests up to 6 months after operation, there was no case of HIV seroconversion. There were three cases of antibody seropositivity to hepatitis B; however, two of these patients were immune preoperatively and the third had a passive transmission of the antibody from massive transfusions. No immediate adverse reactions were observed by the application of fibrin sealant intraoperatively or soon thereafter.

In summary, this study demonstrates in a prospective, randomized fashion the high efficacy of fibrin sealant in achieving local hemostasis in cardiac surgery, as well as its superiority over conventional hemostatic agents. Fibrin sealant reduces postoperative bleeding and therefore decreases the need for emergency resternotomy. Data from a subgroup in this study confirm the extensive European experience, which shows fibrin sealant to be a safe topical hemostatic agent from the point of view of transmission of viral diseases.

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Discussion

Mr. Jaroslav Stark *(London, England).* We have used fibrin sealant (Tisseel, Immuno AG, Vienna, Austria) at The Hospital for Sick Children, Great Ormond Street, in London since 1980 in 206 patients. Sealing of a suture line (aorta–pulmonary artery, coronary artery) during the arterial switch operation was the most common indication (66). Other uses included presealing conduits (40) and their suture lines (28), complex reconstructions of the pulmonary arteries (25), bleeding from the surface of the heart (11), and others (36).

We have not done a prospective study; we have in the past evaluated the results by subjective assessment by an operating surgeon. Excellent results were achieved in 83.5% of cases, good in 14%, and unsatisfactory in 2.5%. The reason for failure of fibrin sealant to control bleeding was our inability to keep the operating field dry. For this reason it is important to plan the use of fibrin sealant carefully. If a period of circulatory arrest is used during the procedure, the anastomosis can be sealed at that time. If bleeding occurs after discontinuation of cardiopulmonary bypass, we use systemic hypotension induced by sodium nitroprusside. This facilitates exposure of a bleeding site and application of fibrin sealant. Pressure may have to be reduced to 40 to 45 mm Hg for a few minutes. Then we keep the pressure at 60 to 70 mm Hg for another hour or two.

In our experience fibrin sealant is an excellent adjunct to hemostasis but it is *not* a substitute for a careful surgical technique.

I would like to ask the authors a question. Did you record what type of bleeding—arterial, venous, or surface of the heart—you were trying to control? Was there any difference in your success rate among these groups?

Dr. Rousou *(Closing).* Fibrin sealant is available in a spray form in Europe, but this was not part of our armamentarium in this multicenter study. I am told by one of the principal investigators, Dr. Sidney Levitsky from the University of Illinois, that he has used it subsequent to the multicenter study in a number of patients quite successfully. It is obviously desirable to have fibrin sealant in spray form.

Another means of controlling arterial bleeders is to lower the blood pressure. We and others have used that technique. However, I cannot quantitate to what extent it has been used in this study.

Dr. Stark, although the collection of data did require investigators to specify whether the bleeding was venous or arterial, I cannot state that it is definitely more effective in venous than in arterial bleeding.