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## Controlled clinical studies of fibrin sealant in cardiothoracic surgery – a review

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**Abstract** *Objective.* More than 2300 clinical papers have been published on the surgical applications of fibrin sealant (FS), with the largest number in the speciality of cardiothoracic surgery. The purpose of this review of the literature was to find and evaluate controlled studies published in the field of cardiothoracic surgery, to clarify the indications and emphasize the benefits of FS available to the practising surgeon.

*Methods.* A database of the surgical publications of FS was created. Up to the end of 1995, at least 24 controlled clinical studies had been published; these may be divided into 20 studies with a positive outcome and 4 studies where the results were not different from the controls. In none of the studies was the clinical result worse after the use of FS.

*Results.* In most of the cardiac studies, FS was successfully used at bleeding sites in reoperations and in congenital heart surgery. Postoperative bleeding may also be reduced by the anterior mediastinal spray application of FS or by preparing woven Dacron prostheses with the sealant. In addition, FS has been found to improve results after type A aortic dissections and, by adding an antibiotic

to the sealant, the postoperative infection rate for active endocarditis of the aortic root can be reduced. In pulmonary surgery FS can be used to reduce pulmonary air leakage, however the results of some studies diverge due to different clinical test conditions and the inclusion of only a small number of patients in the “negative” studies. In none of the controlled studies of esophageal surgery could FS prevent leakage from esophageal anastomoses.

*Conclusions.* Fibrin sealant is safe when it is applied properly, but there is a learning curve for surgeons who start using it. An autologous sealant or a sealant containing human instead of bovine thrombin is preferred, since repeated use of bovine thrombin may induce coagulopathies. The number of controlled clinical studies of FS is currently increasing, with the majority of the papers revealing a beneficial effect of FS when it is used as a hemostatic or sealing agent in cardiothoracic surgery. [Eur J Cardio-thorac Surg (1996) 10:727–733]

**Key words** Fibrin sealants · Cardiothoracic surgery · Controlled studies · Biostatistics

### Introduction

The use of fibrin sealant (FS) in cardiothoracic surgery was pioneered in the mid 1970s. More than 2300 clinical papers have been published on the surgical applications of FS with the largest number in the speciality of cardiothoracic surgery. Despite this large number of publications in

the medical literature, there is still considerable discussion as to the indications, safety and clinical benefits from the use of FS.

The purpose of this review of the literature was to find and evaluate controlled studies published in the field of cardiothoracic surgery, to clarify the indications and emphasize the benefits of FS available to the practising surgeon.

### Fibrin sealant clinical database

A database of more than 2300 publications on the surgical applications of FS was created using Procite bibliographic software. Up to the end of 1995, at least 24 controlled clinical studies had been published in the speciality of cardiothoracic surgery with a mean of 76 patients per study. The study designs included 10 randomized (Table 1) and 14 non-randomized (Table 2) series, which involved a mean of 37 patients (range 7–164) in the treatment group and a mean of 39 patients (range 10–169) as controls. In 20/24 of the controlled studies the authors claimed the outcome with FS was better than in the controls. In 4/24 studies the outcomes were not statistically different from the controls. In no study was the outcome worse in the FS group (Tables 1 and 2).

### Fibrin sealant

The FS used was generally (19/24 of the studies) commercial FS (Tisseel, Beriplast or Biocol) composed of fibrinogen from pooled plasma and a bovine thrombin solution. Almost all of the investigators used 500 units/ml thrombin

and 3000 KIU/ml of aprotinin. Only 1 out of 24 controlled studies [24] utilized single-donor cryoprecipitate to prepare the FS. No serious adverse drug events related to fibrin sealing were reported.

### Reduction of bleeding after reoperation for coronary artery bypass grafting (CABG)

The largest controlled series published was a multicenter study of cardiac reoperations with 164 patients in the FS group, and 169 controls [22]. Fibrin sealant was applied at bleeding sites either directly from the syringe or on a carrier. The results showed a 92.6% success rate for FS in controlling bleeding within 5 min of application, compared with only 12.4% success rate with conventional topical agents ( $P < 0.001$ ). Postoperative blood loss was significantly less ( $P < 0.05$ ) in the FS group than in the matched controls. Additionally, re sternotomy rates after redo operations were significantly lower in the FS group (5.6%) than in a non-matched historical control group (10%) ( $P < 0.0089$ ). It can be argued that there was no adequate control group since the choice of alternative hemostatic agent was left to the discretion of the surgeon. Addition-

**Table 1** Controlled randomized clinical studies in cardiothoracic surgery

Year	Author	Location	Indication/ Measurement parameter	n	Control	n	Outcome	Reference
1989	Rousou	US	Redo CABG/ Resternotomy; hemostasis, blood loss	164	Various conventional hemostats	169	Better haemostat $P < 0.001$ , blood loss $P < 0.05$	22
1990	Fleisher	Canada	Lobectomy; aerostasis	14	Staples No FS	14	$P = 0.94$ No statistical difference	7
1991	Wurtz	France	Partial pulmonary excision; hemostasis aerostasis	25	Electro-coagulation	25	No statistical difference	28
1992	Hsu	Taiwan	Esophageal resection; sealing anastomosis	35	No FS	35	Leaking = same Increase time to leak = better, $P < 0.01$	13
1992	Fékété	France	Esophageal resection reinforcing anastomosis	48	No FS	52	Operative mortality and fistulae, no statistical difference, stenosis better, $P = 0.015$	6
1992	Osterwalder	Switzerland	Pleurodesis for malignant plural effusion; drainage	17	Achromycin	16	Better, no statistics	21
1992	Dahan	France	Pulmonary surgery; drainage and hospitalization time	20	No FS	20	No statistical difference	4
1992	Lozac'h	France	Intrathoracic eso- phagogastric anastomosis	58	No FS	39	No difference	1
1993	Zimmer	Germany	Esophageal varices; sclerotherapy	11	Polidocanol	13	Better, no statistics	30
1993	Mouritzen	Denmark	Pulmonary resection; aerostasis	31	Surgery alone	32	Better, $P < 0.02$	18

**Table 2** Controlled non-randomized clinical studies in cardiothoracic surgery

Year	Author	Location	Indication measurement parameter	n	Control	Historical control groups	n	Outcome	Reference
1981	Köveker	Germany	Aortoventriculoplasty, sealing cardiac Dacron prosthesis; operation time, post-op blood loss	16	Blood	–	16	Better (both outcomes), $P < 0.05$	15
1986	Huth	Germany	Sealing cardiac patches & suture lines; blood loss	57	No FS	+	20	Better, $P < 0.01$	14
1987	Spotnitz	US	Perioperative hemostat (CABG etc)	20	No FS	+	20	Better, $P < 0.05$	24
1987	Thetter	Germany	Recurrent pneumothorax or lung resection; reduced drainage period	21	No FS	–	15	Better, no statistics	26
				Pneumo-thorax, 20 lung resection					
1987	Hartel	Germany	Pulmonary resection; aerostasis	10	No FS	–	11	Better, no statistics	
					FS + sutures versus sutures alone	–	10	Better, $P < 0.001$	12
1988	Gotti	Italy	Partial pulmonary resection; aerostasis	44	No FS	+	121	Better, $P < 0.1$	9
1988	Tanemoto	Japan	Cardiac procedures; drainage	31	Sutures	–	26	Better, $P < 0.01$	25
1989	Grunenwald	France	Lobectomies, pneumothorax, decortications; aerostasis	124	No FS	+	79	Better, no statistics	11
1991	Séguin	France	Aortic dissection Type A hemostat	18	Sutures & Dacron	–	14	Better, $P < 0.01$	23
1991	Yasuda	Japan	Closure post-op pleuropulmonary fistula	20	No FS	–	24	Better, no statistics	29
1992	Burgos	Spain	Cardiovascular reoperation; hemostasis	55	Other pleural adhesives First operation control, Reoperation control	–	60	Better (versus reoperation control), $P < 0.01$	3
1992	Gotti	Italy	Bronchial stump protection; broncho-pleural fistula incidence	39	Pedunculated patch + FS versus patch alone	–	66 50	Better, no statistics	10
1994	Omote	Japan	Pulmonary resection; post-operative air leakage	7	No FS	+	29	Better, no statistics	20
1994	Watanabe	Germany	Infective endocarditis, aortic valve replacement, antibiotic (neomycin) in fibrin sealant; reduction of infection	25	No antibiotic FS	–	48	Better early mortality, $P < 0.05$ Better infection-related complications, $P < 0.05$ Better late mortality, $P < 0.05$	27

ally, Tissel was applied either directly to the bleeding site or in combination with a carrier, and in one center the protocol allowed for FS application while the patient was still fully heparinized. Thus there was variability in both test and control treatments across centers. It is not generally believed that bleeding time is a valuable indicator of clinical utility, and the investigators found no significant reduction in the number of transfused blood products as compared to historical controls.

Burgos [3] confirmed the results in another study of 181 patients; group I ( $n=60$ ) with first time cardiopulmonary bypass was used as the control; group II ( $n=55$ ) consisted of reoperated patients in whom FS was sprayed at the pleuropericardial surface and group III ( $n=66$ ) reoperated patients in whom FS was not used. In the analysis of the results, 14 patients were excluded owing to immediate reoperation due to bleeding. The amount of postoperative bleeding was  $855 \pm 369$  ml in group I,  $1153 \pm 759$  ml in group II and  $1995 \pm 430$  ml in group III. The statistical comparison of the three groups revealed a significant difference between groups II and III ( $P < 0.01$ ).

#### Reduction of bleeding by anterior mediastinal spray application of fibrin sealant during cardiac operations

Spotnitz [24] found a significant reduction of perioperative hemorrhage by anterior spray application of FS during cardiac operations. In 20 consecutively treated patients, FS was sprayed on the anterior mediastinum before closure of the median sternotomy incision. A control group of 20 patients undergoing identical cardiac operations (CABG and valve replacements including one reoperative procedure) by the same surgeon within a 1-year period was chosen for comparison of chest tube outputs. The differences between control and spray chest tube output was at most 300 ml, however it was statistically significant at both 12 and 24 h.

Tanemoto [25] evaluated the effectiveness of FS in cardiac surgery using a similar technique where the sealant was sprayed at the anterior mediastinum. They found a significant reduction in chest tube drainage in patients where FS was used, after both 1 and 24 h following admission to the ICU, however the drainage was in general low in both groups of patients, and the difference did not exceed 300 ml. They concluded that the use of FS in the anterior mediastinum was particularly advantageous in the control of oozing bleeding.

#### Reduction of bleeding in congenital heart surgery

Huth [14] compared 21 patients who underwent surgical repair of tetralogy of Fallot and 10 patients who underwent a Senning operation for transposition of the great arteries with patients who had undergone the same opera-

tion without FS one year earlier. After a marked reduction of postoperative blood loss through the application of FS had been demonstrated in this first study, the results obtained using FS to achieve local hemostasis during surgery in 52 other patients (36 with tetralogy of Fallot, 16 with transposition of the great arteries) were added. They found that FS reduced postoperative blood loss after intracardiac repair of tetralogy of Fallot and the Senning operation for transposition of the great arteries by securing local hemostasis in patches and suture lines, and they felt that the general reduction of postoperative bleeding lead to better identification of bleeding complications requiring reoperation.

#### Reduction of bleeding from vascular prostheses used in cardiothoracic surgery

Köveker et al. [15] used FS successfully as an adjunct to control diffuse myocardial bleeding and bleeding from suture-holes, and as a sealant of woven Dacron prostheses. They performed a controlled clinical study in 32 patients who underwent aortoventriculoplasty operations with prosthetic enlargement of the left and right ventricular outflow tracts. In the first 16 patients a conventional blood preclotting procedure was used, while in the last 16 consecutive patients the woven Dacron patch was sealed with FS. They found that the operation time was shortened by more than one third in the FS group of patients (178 min versus 115 min,  $P < 0.05$ ), and a reduction of postoperative blood loss was found after 24 h as well as after 72 h. The 24-hour data (13.9 ml/kg body weight versus 18.6 ml/kg) showed a statistically significant difference ( $P < 0.05$ ). The difference in blood loss after 72 h between the groups (11.9 ml/kg versus 13.5 ml/kg) was not significant ( $P > 0.05$ ). They concluded that the sealing of woven Dacron prostheses with FS is superior to the conventional preclotting method.

#### Improved results after operation of type A aortic dissections

Séguin [23] studied 42 patients who had isolated replacement of the ascending aorta for type A dissection: group 1 ( $n=10$ ) had replacement of the ascending aorta with an intraluminal sutureless graft, group 2 ( $n=14$ ) had a Dacron prosthesis sutured to the aorta, and in group 3 ( $n=18$ ) the proximal and distal aortic stumps were glued together and reinforced at the suture sites with FS before implantation of the Dacron prostheses. Perioperative blood loss during the first 24 h was significantly lower in group 3, and total hospital mortality was 70% in group 1, 43% in group 2, and 5.5% in group 3. They concluded that the use of FS reduced perioperative deaths, perioperative bleed-

ing, and in-hospital mortality, and improved the results of operation for acute aortic dissection.

#### Reduced infection rate after operation for active endocarditis of the aortic root

Watanabe [27] used an antibiotic fibrin compound in operations for active endocarditis of the aortic root in 25 patients and compared the results with 48 patients where FS was not used. Neomycin sulfate, 10 mg, and FS, 4 ml, were mixed. After debridement of the infected tissue, antibiotic-FS was injected into the abscess cavities. The sewing rings of prosthetic valves and the Dacron graft in composite grafts were also soaked with antibiotic-FS before implantation. The early mortality was 2/25 in the antibiotic-FS group as compared to 13/48 in the control group ( $P < 0.05$ ). Infection related death was 1/25 in FS, versus 11/48 in the control, group ( $P < 0.05$ ). Residual of recurrent endocarditis was 1/25 versus 6/48 (NS). The authors concluded that the antibiotic-FS compound appears to be an efficient prophylactic tool in preventing postoperative residual endocarditis and serious infection-related complications.

#### Reduction of pulmonary air leakage after lung resection

The largest prospective series of 124 operations complicated by major air leakages which were treated with application of FS was reported by Gruenwald [11]. The treated group was compared to a similar group of operated patients conducted by the same surgeon, where FS was not used. The duration of postoperative thoracic drainage was markedly reduced (on average, 2 days) and the patient postoperative hospital stay was shortened. The authors concluded that the intraoperative use of FS reduces the frequency of respiratory complications following lung surgery. Mouritzen [18] investigated the effect of FS on the treatment or prevention of air leakages in 114 patients undergoing pulmonary resections and pneumonectomies. Intraoperatively, 81% of the patients undergoing pulmonary resection who suffered from air leakages after conventional suturing showed improved results of the airway-tolerance-pressure test after the application of FS (one-sided probability value  $< 0.01$ ; 95% confidence interval: 58–95%). Treatment with FS reduced the incidence of postoperative leakages significantly from 66% in the control group to 39% in the treatment group (one-sided probability value  $< 0.02$ ; estimated risk reduction 41%; 95% confidence interval 2–65%). In a smaller number of studies the investigators have also found FS to be effective in reducing postoperative air leakage [9, 12, 20, 26], however at least three studies showed no statistical difference between the treated group and controls, although the trend favored the FS group of patients [4, 7, 28].

#### Closure of bronchial stump fistula and pleurodesis

In a few controlled studies FS has been effective for closure of persistent pleuropulmonary fistula after a thoracic surgical procedure [23] and for pleurodesis of malignant pleural effusions, although it was not better than tetracycline pleurodesis [21]. Fibrin sealant was found to be effective in protecting the bronchial stump in the early postoperative period, however the incidence of late bronchopleural fistula was the same in the FS group as in a group where a pleural patch was used for protection of the bronchial stump [10].

#### Leakage of esophagogastric anastomoses after esophageal resection

Fibrin sealant was evaluated by Hsu [13] as a sealant of the esophagogastric anastomosis to prevent leaks in 35 patients and 35 controls. The esophagogastric anastomosis was placed on the neck. The rate of leakage between the two groups had no statistical significance ( $P > 0.05$ ). The average time to leakage was  $7.6 \pm 1.07$  (mean  $\pm$  SD) in the FS group, and  $5.09 \pm 0.94$  days in the control group. The difference was statistically significant ( $P < 0.01$ ). The authors concluded that using FS could not prevent leakage of the esophagogastric anastomosis, but could delay the time of leak.

Fékété [6] studied 100 patients who had esophageal anastomosis. Fibrin sealant was used to reinforce the anastomosis in 48 of these patients and compared to a control group of 52 patients. The mortality, the number of fistulae and their severity were not statistically different in the two groups, but no stenoses were found in patients who had FS, whereas the rate of anastomotic stenosis was 13.5% in the controls. The authors could not give a precise explanation for this.

Lozac'h [16] studied 97 patients with esophageal cancer who had an intrathoracic esophagogastric anastomosis. They found the incidence of postoperative fistulae to be similar in the two groups but reoperations were more frequent in the control group where no FS was used. They concluded, however, that the number of patients in the trial was too small to draw valid conclusions.

#### Sclerosis of esophageal varices

Zimmer [30] compared FS ( $n = 11$ ) to polidocanol ( $n = 13$ ) in endoscopic sclerotherapy of esophageal varices after bleeding, and found the obliteration of varices to be higher in the FS group (72%) as against the polidocanol group (54%). The authors concluded that by using FS, as opposed to polidocanol, a higher obliteration rate could be achieved with a considerably lower risk of complications.

## Discussion

In general, the benefits of FS in cardiothoracic surgery are many, but it must be applied properly to avoid potential problems, and there is a learning curve for surgeons who start using FS. During cardiopulmonary bypass when the patients are fully heparinized FS may still be efficient [22], however the cardiotomy sucker should not be used near the FS to avoid introducing thrombin into the bypass circuit, where it may clot in the filters. In addition, FS should not be used intravascularly (e.g., in the heart during valve operations or aneurysm reconstructions), because it could cause a systemic embolus. An initial concern with FS was that it might lead to dense adhesions, making subsequent operations far more difficult. However, several studies have found that FS does not increase adhesions and may, in fact, decrease them [17].

Based on this review of controlled clinical studies, it could be recommended that FS be used in redo CABG, since it has been proven to reduce postoperative blood loss and decrease the incidence of emergency re sternotomy. However, these controlled studies were conducted before the use of systemic aprotinin, which may halve the postoperative blood loss, and it is not known today if FS is more efficient than systemic aprotinin, except at localized, oozing bleeding sites (e.g., anastomoses). Although controlled studies have shown a significant reduction of perioperative hemorrhage using anterior mediastinal spray applications of FS during first time CABG and valve operations, the reduction in bleeding did not exceed 300 ml, which is most often not clinically significant since this amount may not increase the requirement for blood transfusions. Therefore the cost-benefit of FS in first time uncomplicated cardiac surgery needs to be defined. In infants, on the other hand, the blood loss may be more significant, and FS did reduce postoperative blood loss after intracardiac repair of tetralogy of Fallot and the Senning operation by securing local hemostasis in patches and suture lines. Unfortunately the investigators did not report if there was a decrease in the total amount of blood used during the operations.

Fibrin sealant is more efficient and faster than conventional preclotting with blood for the sealing of woven Dacron prostheses, which were often used in cardiovascular surgery. It did improve the results after operation of type A aortic dissections in one study, and an antibiotic-FS compound was successfully used to reduce the infection-related mortality in surgery for active endocarditis of the aortic root; however these individual studies need to be confirmed by others before general recommendations can be made.

Repair of surgical defects of lung parenchyma is traditionally accomplished by suture techniques or stapling devices. Both of these methods damage adjacent healthy lung parenchyma [1], and tissue adhesives have been applied to lung surgery in an attempt to salvage tissue and create an airtight closure, since persistent air leak after pulmonary

resections leads to extended hospitalization and increased costs. The use of FS as a sealant of pulmonary air leakage is controversial, however, since at least three studies showed no difference between the treated group and controls, although the trend in these studies favored the FS group of patients [4, 7, 28]. The reason that the majority of the studies had a positive outcome while a few studies were "negative" may be the small number of patients included in the negative studies [8], and the clinical end points used which were not the same in all studies. To draw a conclusion from these controlled studies, we believe that FS may reduce pulmonary air leakage if it is properly applied with a spray system to a dry lung surface without bleeding or air leakage at the time of the application. This means that the lung should not be ventilated for 1–2 min while the sealant is allowed to cross-link. Major air leaks from bronchi should be sewn before glueing, otherwise the sealant will burst off from the lung.

The fact that FS has not been successful as a sealant of esophagogastric anastomoses may reflect the theory that anastomotic leakage is not only a mechanical problem but may be caused by ischemia and, based on this literature study, we do not recommend that FS be used for esophagogastric anastomoses.

In the United States the introduction of the commercially available FS (Tisseel, Immuno AG and Beriplast, Behringwerke AG) was prevented by the Food and Drug Administration ruling in 1978 banning products derived from pooled human fibrinogen [5]. There have not been any reports of viral infection transmitted by Tisseel, despite more than one million clinical applications of the product [17] and no serious adverse effects or complications as a result of the use of FS have been reported in the present survey. However, the studies in general lack longer term follow-up to make valid conclusions on safety issues, and only a few investigators have focused on the occurrence of postoperative coagulopathies, which may be an adverse antibody-mediated reaction to repeated use of bovine thrombin [2, 19]. Although most manufacturers are in the process of switching from bovine thrombin to thrombin derived from pooled human plasma, the number of publications discussing the need for the use of autologous FS is increasing, with questions of safety highlighted. The possible reactions to high doses of exogenous thrombin in both the commercial products and sealants with autologous fibrinogen concentrates, however, clearly suggest the desirability of the future development of a totally autologous FS.

Fibrin sealant was introduced into surgery more than 20 years ago. Based on our literature studies, we have found that cardiothoracic surgeons lead in the performance of controlled clinical studies with FS, however we think that even more controlled studies would be desirable and improvements could possibly be achieved by the following precautions: 1. randomization, 2. an increase in the number of patients and calculation of confidence limits in "negative" clinical trials, 3. focus on safety issues by longer

term follow-up, 4. definition of the cost-benefit, 5. clarification of whether FS is more efficient in combination with a carrier. In conclusion, the number of controlled clinical

studies is increasing, with the majority of the papers disclosing a beneficial effect when FS is used as a hemostatic or sealing agent in cardiothoracic surgery.

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