REVIEW ARTICLE

Use of Fibrin Sealants in Cardiovascular Surgery: A Systematic Review

John A. Rousou, M.D.

Division of Cardiac Surgery, Baystate Medical Center, Springfield, Massachusetts

ABSTRACT ***Background:*** **Fibrin sealants are used for hemostasis and tissue adherence.** ***Aim of Study:*** **This systematic review summarizes published clinical data for fibrin sealant use in cardiovascular surgery.** ***Methods:*** **A literature search for the following terms was conducted using PubMed and EMBASE: (TISSEEL or Tissucol or Beriplast P or Evicel or Quixil or Crosseal or Reliseal or Fibringluraas or Bolheal or Tachosil or Vivostat or Vitagel or Artiss or ''fibrin glue'' or ''fibrin sealant'' or ''fibrin tissue adhesive'') and (cardiac or cardiovascular or vascular or heart or coronary or surgery). Case reports and series were excluded; although reports of controlled trials were preferred, uncontrolled trial data were also considered.** ***Results:*** **Clinical trials and chart review analyses of fibrin sealants were identified and summarized. Although clinical trial data were available for other agents, the majority of published studies examined TISSEEL. Overall, TISSEEL and other fibrin sealants showed improvements over standard of care or control groups for a variety of predefined endpoints. Safety findings are also summarized.** ***Conclusions:*** **Data from these studies showed that fibrin sealants were well tolerated and provided effective hemostasis in a range of cardiac and aortic surgeries.** doi: 10.1111/jocs.12099 *(J Card Surg 2013;28:238–247)*

INTRODUCTION

Fibrin sealants, sometimes referred to as fibrin glues, are topical hemostatic agents that are a source of fibrinogen and thrombin, and thereby will promote the final stage of the coagulation cascade—the formation of a fibrin clot and network for the subsequent healing process.[1] Fibrin sealants provide hemostasis and tissue adhesion, which is advantageous in many clinical situations.[2,3] They have been used primarily for adjunctive hemostasis in a variety of settings, including cardiovascular and aortic procedures[4–8] and carotid endarterectomy.[9,10]

Clinical trials have shown that fibrin sealants have been successful in improving outcomes compared with standard techniques in patients with a wide range of cardiovascular conditions.[7,11–13] For example, in coronary artery bypass graft (CABG) surgery, fibrin sealant agents are used as adjunctive hemostatic agents to control bleeding from distal or proximal anastomoses (Fig. 1A), to control diffuse epicardial bleeding (Fig. 1B), and to seal the internal mammary artery bed (Fig. 1C). Fibrin sealants may also be applied on sternal edges to control profound bone marrow bleeding (Fig. 1D). Patients undergoing cardiac reoperation, thoracic organ transplantation, aortic aneurysm surgery, and complex congenital heart surgery are also candidates for use of fibrin sealants.[14] The aim of this systematic review is to summarize the published clinical data that are pertinent to the use of fibrin sealants in cardiovascular surgery.

METHODS

A detailed search of the literature was conducted using PubMed and EMBASE, for the years 1979–2012. The following terms were searched in the title/abstract: (TISSEEL or Tissucol or Beriplast P or Evicel or Quixil or Crosseal or Reliseal or Fibringluraas or Bolheal or Tachosil or Vivostat or Vitagel or Artiss or ''fibrin glue'' or ''fibrin sealant'' or ''fibrin tissue adhesive'') and (cardiac or cardiovascular or vascular or heart or coronary or surgery). Studies that evaluated nonfibrin sealants or glues were excluded. Case reports and series were discarded, and the bibliographies of reviews were assessed for appropriateness of inclusion. Although randomized controlled trials were the preferred data source, the results of uncontrolled trials were also considered in the absence of controlled data in a particular setting. All publications included were analyzed for clinical relevance and statistical validity when appropriate.

Conflict of Interest: Dr. Rousou has received consulting fees from Baxter Healthcare Corporation. Editorial support for the preparation of this manuscript was funded by Baxter Healthcare Corporation. The author had full control of the content of this article.

Grant sponsor: Baxter Healthcare Corporation.

Address for correspondence: John A. Rousou, M.D., Baystate Medical Center, North Campus, 759 Chestnut Street, Suite 4628, Springfield, MA 01107. Fax: 413-794-4212; e-mail: jrousou@comcast.net

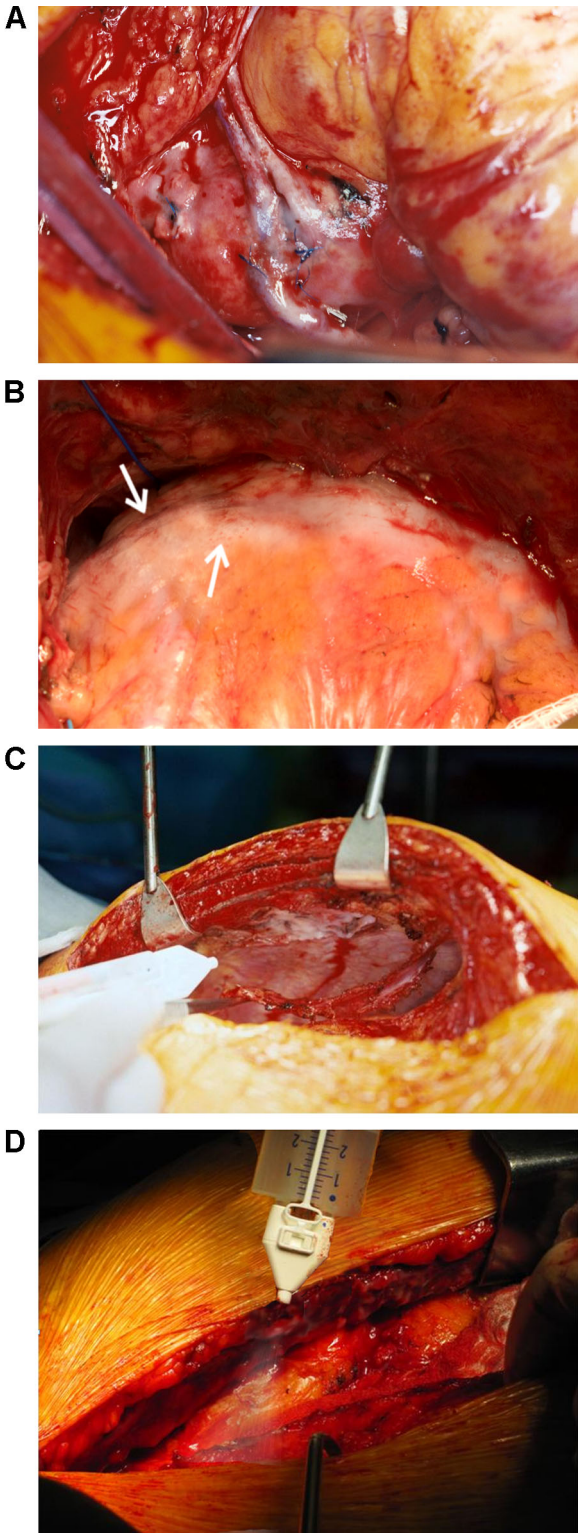

Figure 1. *Example of fibrin sealant used (A) on proximal vein graft anastomoses to control needle-hole bleeding secondary to intake of Plavix, (B) to control diffuse epicardial bleeding in redo coronary artery bypass grafting, (C) to seal the internal mammary artery bed in a coagulopathic patient undergoing coronary artery bypass grafting, and (D) to seal sternal edges and control diffuse bone marrow bleeding in an elderly osteoporotic patient.*

Fibrin sealants have been used in numerous cardiovascular procedures. For the purposes of this review, these were divided into two categories:

- Major cardiac/cardiovascular surgery (CABG, valve replacement and other procedures, repair of ventricular septal defects [VSDs], management of infective endocarditis).
- Aortic surgery (replacement of the ascending aorta, aortic dissection, aortic aneurysm).

RESULTS

Efficacy in major cardiac surgery

The majority of publications found suitable for major cardiac surgery pertained to TISSEEL (Baxter Healthcare Corporation, Westlake Village, CA, USA) and the remaining publications described clinical trials pertaining to the use of Beriplast P (CSL Behring, GmbH, Marburg, Germany), Fibringluraas (Shanghai RAAS Blood Products Co, Ltd, Shanghai, China), and Vivostat (Vivolution A/S, Birkeroed, Denmark) in cardiovascular surgery (Table 1).

The efficacy of the fibrin sealant Fibringluraas was examined in a recent randomized prospective trial in elderly patients undergoing on-pump CABG.[15] Patients who received Fibringluraas lost 326.2 mL of blood (chest tube drainage), compared with 516.0 mL in patients who received bone wax as a control ($p = 0.001$). Patients in the Fibringluraas group also received less blood products (3.6 and 5.5 U of packed red blood cells [PRBCs] and fresh frozen plasma [FFP], respectively) compared with patients in the bone wax group (7.4 and 9.0 U of PBRC and FFP, respectively; both $p = 0.001$). Patients also had a shorter hospital stay in the Fibringluraas group compared with controls (10.5 vs. 11.0 days; $p = 0.045$). Rates of complications and mortality were similar between the two groups.[15]

The efficacy of TISSEEL in major cardiac surgery has been investigated in two randomized controlled trials. The more recent trial found that the vapor-heated solvent/detergent-treated TISSEEL VH S/D formulation was at least as efficacious as the previous vapor-heated TISSEEL VH formulation in achieving hemostasis at the primary treatment site within 5 minutes (88.2% vs. 89.6%, respectively) and in maintaining hemostasis until surgical closure.[16] Comparison of TISSEEL with conventional topical hemostatic agents in patients undergoing emergency resternotomy or cardiac reoperation found that TISSEEL stopped bleeding within 5 minutes of application in 92.6% of cases, but in only 12.4% of historical matched control cases treated with conventional topical agents ($p < 0.001$).[7] Compared with nonmatched historical controls in this study, TISSEEL was associated with significantly lower rates of resternotomy after cardiac reoperation (5.6% vs. 10.0%; $p = 0.0089$).[7]

Smaller prospective trials have demonstrated the efficacy of fibrin sealants in a variety of procedures and populations. A technique involving sealing the Dacron

J CARD SURG
2013;28:238–247

TABLE 1
Summary of Publications Featuring Use of Fibrin Sealants in Major Cardiovascular Surgery

Citation	Sealant Name	Use	Study Design	Patients, n	Comparator	Study Strengths/ Weaknesses: Main Result
Prospective						
Yu et al.[15]	Fibringluraas	Patients undergoing median sternotomy and on-pump CABG	Prospective, randomized	82	Bone wax	Prospective, randomized study Direct injection of fibrin sealant was safe and effective in reducing 24-hour postoperative blood loss in senior patients
Lowe et al.[16]	TISSEEL	Cardiac surgery requiring cardiopulmonary bypass and median sternotomy	Prospective double-blind, RCT, multiple centers in the United States	288	TISSEEL VH S/D versus TISSEEL VH	Prospective, randomized, double-blind study TISSEEL VH S/D is at least as efficacious as TISSEEL VH and has similar safety profile
Farhat et al.[17]	TISSEEL	Prosthetic valve placement for active endocarditis	Prospective, nonrandomized, uncontrolled in a French center	16	None	Small sample size Prostheses sutured with antibiotic plus TISSEEL were associated with 94% actuarial survival rate and 92% freedom from reoperation
Hanks et al.[18]	Vivostat	Cardiothoracic (29%), general, obstetric/ gynecologic, vascular	Prospective, randomized, multicenter	69	Surgicel	Randomized Small number of patients; not all patient-related factors were controlled Rates of successful hemostasis were significantly higher in the Vivostat group compared with the Surgicel group; time to hemostasis was shorter in the Vivostat group
Codispoti and Mankad[19]	Beriplast P	Repair of congenital heart defects	Prospective, randomized	52	No intervention	Randomized, single institution Small number of participants Effective in decreasing blood loss in pediatric patients undergoing open-heart surgery
von Segesser et al.[11]	TISSEEL	Repair of VSD	Prospective, nonrandomized, controlled in a Swiss center	36	PTFE patch and running sutures reinforced with pledgets	Controlled study Small sample size TISSEEL sealing of patch was associated with significantly lower incidence of residual VSDs
Leca et al.[20]	TISSEEL	Repair of VSD	Prospective, nonrandomized, uncontrolled in children in a French center	15	None	Patients with multiple VSDs No reoperations for residual VSD; good long-term results
Rousou et al.[7]	TISSEEL	Reoperative cardiac surgery or emergency resternotomy	Prospective RCT, multiple centers in the United States	333	Conventional topical hemostatic agents; also made comparisons with historical control groups for secondary endpoints	Prospective, randomized study TISSEEL was safe and effective for control of localized bleeding and superior to conventional agents

TABLE 1
Continued

Citation	Sealant Name	Use	Study Design	Patients, n	Comparator	Study Strengths/ Weaknesses: Main Result
Retrospective						
Lamm et al.[21]	TISSEEL	Open-heart coronary bypass and/or valve surgery	Retrospective chart review in a German center (November 1995–December 2000)	2716	TISSEEL versus no fibrin sealant	Large patient population Retrospective analysis; model carried a risk of a treatment and selection bias, requiring independent confirmatory analysis TISSEEL was associated with a significant increase in mortality and myocardial damage
Goerler et al.[22]	TISSEEL	Open-heart coronary bypass and/or valve surgery	Retrospective controlled chart review in a German center (July 1999–December 2002)	2149	TISSEEL versus no fibrin sealant	Large patient population Retrospective analysis; intraoperative findings were not considered in the prediction of operative mortality TISSEEL was associated with a significant increase in 30-day mortality rate
Kieser et al.[23]	TISSEEL	Open-heart coronary bypass and/or valve surgery	Retrospective, controlled chart review in a Canadian center (September 1988–June 1990)	289[a]	TISSEEL versus no fibrin sealant[a]	Consecutively used in all patients; not limited to high-risk patients Retrospective analysis TISSEEL was associated with significant reductions in blood loss and reoperation for bleeding
Huth et al.[24]	TISSEEL	Correction of ToF and Senning procedure in TGA	Retrospective	21	No treatment	Retrospective analysis Small patient numbers Blood loss immediately postoperatively was lower with TISSEEL compared with control

[a]The treatment groups included patients who received no TISSEEL (n = 96), those who received TISSEEL (n = 96), and those who received TISSEEL in surgeries performed 1 year after the initial group (n = 97). CABG, coronary artery bypass graft; PTFE, polytetrafluoroethylene; RCT, randomized controlled trial; S/D, solvent/detergent treated; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; VH, vapor heated; VSD, ventricular septal defect.

sewing ring of a prosthetic valve with an antibiotic/TISSEEL mixture was shown to be effective as adjunct therapy in the surgical treatment of active endocarditis (actuarial survival rate at one year, 94%; freedom from reoperation, 92%).[17] Vivostat, when compared with oxidized cellulose (Surgicel) in a randomized trial examining patients undergoing a variety of surgeries, including cardiothoracic (29% of patients), resulted in higher rates of hemostasis, with ~95% of patients overall achieving hemostasis at 5 minutes in the Vivostat group compared with ~60% of patients in the Surgicel group ($p < 0.0001$). Shorter times to hemostasis were also observed in the Vivostat group compared with the Surgicel group (1.6 vs. 3.3 minutes; $p < 0.0001$).[18] In a randomized controlled trial, Beriplast P significantly reduced intraoperative blood loss compared with no intervention (26 vs. 65 mL/kg; $p \leq 0.01$) in pediatric patients receiving open-heart surgery. Postoperative blood loss at 24 hours was also lower in the Beriplast group as compared with the control group (23 vs. 31 mL/kg; $p \leq 0.05$).[19]

A controlled, nonrandomized trial comparing VSD closure either using a polytetrafluoroethylene (PTFE) patch and running sutures reinforced with pledgets or sealing the suture line of the PTFE patch with TISSEEL reported a significantly lower incidence of residual VSDs in the TISSEEL group (5 of 14 [36%] patients; $p < 0.05$) than in the reinforced-sutures group (16 of 22 [72%] patients).[12] In addition, the mean diameter of any residual VSDs was significantly smaller in the TISSEEL group. TISSEEL has also been shown to be effective in repairing multiple VSDs in children, with good short- and long-term results.[20] Other reports describing TISSEEL use in major cardiac surgery include retrospective controlled studies that supported the ability of TISSEEL to reduce blood loss (assessed using chest tube

outputs) during open-heart surgery in adult[23] and pediatric patients.[24]

Efficacy in aortic surgery

The majority of publications in aortic surgery pertained to TISSEEL, and the remaining publications described clinical trials pertaining to the use of TachoSil (Nycomed Austria, Linz, Austria), and Bolheal (Chemo-Sero Therapeutic Institute, Kumamoto, Japan) (Table 2).

The use of TISSEEL in conjunction with synthetic cyanoacrylate surgical glue has been successful in the translumbar embolization of type II endoleaks that occurred after endovascular repair of abdominal aortic aneurysm (AAA).[25] The thrombization technique was associated with a significantly lower risk of type II endoleak (incidence, 2.2% vs. 15.2%; hazard ratio, 0.13; $p < 0.0001$). Similarly, TachoSil was effective in controlling suture-hole bleeding in patients with intact infrarenal AAA in a small, randomized, controlled trial.[26] Compared with patients who received standard compression with surgical swabs, TachoSil significantly shortened the time to hemostasis (264 vs. 408 sec; $p = 0.026$), reduced blood loss during the operation (503 vs. 615 mL; $p < 0.001$) and after cross-clamp removal (26.5 vs. 45.4 g; $p < 0.001$), and reduced drainage volume at 36 hours postoperation (116.7 vs. 134.5 mL; $p = 0.034$).[26]

A prospective, nonrandomized study demonstrated successful aneurysm sac embolization using TISSEEL at the time of endografting in 83 of 84 patients (99%) with AAA.[27] The mean maximum transverse aneurysm diameter was significantly reduced (50.4 vs. 42.0; $p = 0.0001$), and there was a low rate of delayed type II endoleak (2.4%). Moreover, of the 31 patients who were available for follow-up 24 months after the procedure, 14 (45.2%) showed a reduction in maximum transverse aneurysm diameter of $\geq$5 mm, 16 (51.6%) had no significant changes, and 1 patient showed a >5-mm enlargement.[27] A small, short-term, prospective, randomized comparison of TISSEEL and autologous fibrin sealant in patients undergoing replacement of the ascending aorta found no adverse effects with either preparation.[28] The overall efficacies of the two preparations were comparable (Table 2), although the surgical time and volume of colloids used were significantly lower in the autologous fibrin sealant group.

A single-center, randomized study examining the ''rub-and-spray'' method for applying Bolheal to anastomoses in patients receiving emergency replacement of the ascending aorta or the ascending-hemiarch found that Bolheal significantly reduced the median time to hemostasis compared with the control group who did not receive fibrin sealant (41.5 vs. 51.0 minutes; $p = 0.036$).[29] Mean blood loss was significantly lower in the Bolheal group during both the hemostatic (99 vs. 257 mL; $p = 0.016$) and the 12-hour postoperative periods (268 vs. 526 mL; $p = 0.054$).[29] A randomized trial comparing TachoSil to conventional hemostatic fleece in patients undergoing mainly aortic, but also cardiac, surgery found that 75% of patients receiving TachoSil achieved hemostasis at 3 minutes, compared with 33% of patients receiving standard treatment ($p < 0.0001$).[30] A greater proportion of patients achieved hemostasis at 6 minutes with TachoSil, as compared with control.[30]

A retrospective study compared results of standard endovascular aneurysm repair of AAA in 224 consecutive patients with results of endovascular repair with addition of a preventive aneurysmal sac clotting technique in 180 consecutive patients.[31] The preventive sac clotting technique, termed ''thrombization'' by the authors, involved injection of TISSEEL (with or without embolization microcoils) into the aneurysm sac. The thrombization technique was associated with a significantly lower risk of type II endoleak (incidence, 2.2% vs. 15.2%; hazard ratio, 0.13; $p < 0.0001$).[31] A small retrospective study involving patients with nonruptured AAA managed using endovascular aneurysm repair compared the incidence of type II endoleak in patients in whom TISSEEL had been injected into the aneurysm sac at the end of the procedure and those in whom it had not (mean follow-up, 18.5–20.0 months).[13] The incidence of type II endoleak was significantly lower with TISSEEL (5.5% vs. 30.0%; $p = 0.05$). The TISSEEL group also underwent significantly fewer abdominal computed tomography studies per year (1.2 vs. 2.0; $p = 0.05$), although the number of minutes of X-ray exposure was comparable in the two groups (32.3 vs. 30.0 minutes, respectively).[13]

Two retrospective, comparative studies have compared the use of TISSEEL with other procedures in the surgical management of type A acute aortic dissection.[11,32] The first of these retrospective comparative studies (follow-up, 6 months to 6.5 years) compared three procedures: (1) intraluminal sutureless graft, (2) Dacron prosthesis sutured to the aorta, and (3) proximal and distal aortic stumps glued together and reinforced at the suture sites with TISSEEL before implantation of the Dacron prosthesis.[11] The Dacron prosthesis/fibrin sealant technique group had significantly less blood loss in the first 24 postoperative hours than the other two groups (355 vs. 755 mL for intraluminal sutureless graft [$p < 0.05$] and 1055 mL for Dacron prosthesis [$p < 0.01$] groups, respectively), as well as substantially lower operative (0% vs. 30% and 29%) and in-hospital (5.5% vs. 70% and 43%) mortality. The one death that occurred in the Dacron prosthesis/TISSEEL group was due to septicemia. More recently, the durability of three techniques for aortic root reconstruction (valve resuspension with reinforcement of the aortic root with Teflon felt, gelatin-resorcinol-formaldehyde [GRF] glue, or TISSEEL) was evaluated by Casselman et al.[32] This 10-year retrospective study found that use of the fibrin sealant was an independent risk factor for aortic root reoperation; the incidence of reoperation at 10 years in the TISSEEL group was 40% versus 23% with Teflon felt and 11% with GRF glue. Similarly, a small, uncontrolled, retrospective study ($n = 6$) reported successful repair of type A aortic dissection using TISSEEL in the aortic arch, which was the site of the initial tear.[33] The authors concluded that this technique

TABLE 2
Summary of Publications Featuring Use of Fibrin Sealants in Aortic Surgery

Citation	Sealant Name	Use	Study Design	Patients, n	Comparator	Study Strengths/ Weaknesses: Main Result
Prospective						
Maisano et al.[30]	TachoSil	Elective heart surgery, ascending aorta or arch	Prospective, randomized, open-label, multiple centers across Europe	120	Standard treatment (hemostatic fleece)	Randomized, international More patients treated with TachoSil achieved hemostasis at 3 minutes compared with standard treatment
Bajardi et al.[26]	TachoSil	Abdominal aortic aneurysm	Prospective, randomized, single center	20	Standard compression with surgical swabs	Randomized Small number of participants Successfully controlled suture-hole bleeding during vascular reconstruction using Dacron grafts
Minato et al.[29]	Bolheal ''Rub-and-Spray'' method	Emergency replacement of ascending aorta or ascending hemiarch	Prospective, randomized, single center	20	No fibrin sealant	RCT Single center, small patient population Bleeding, bleeding risk, and time to hemostasis were significantly reduced compared with control
Zanchetta et al.[27]	TISSEEL	Endovascular repair of abdominal aortic aneurysm	Prospective, nonrandomized, uncontrolled in an Italian center	84	None	Prospective Small sample size Aneurysmal sac embolization with TISSEEL was successful in 99% of cases and had a low rate (2.4%) of delayed type II endoleak
Christenson and Kalangos[28]	TISSEEL	Replacement of ascending aorta	Prospective, randomized, controlled in a Swiss center	20	Autologous fibrin sealant	RCT Small sample size TISSEEL and autologous fibrin sealant had similar overall efficacy
Retrospective						
Pilon et al.[13]	TISSEEL	Endovascular repair of abdominal aortic aneurysm	Retrospective, nonrandomized, controlled chart review in an Italian center (January 2005–February 2008)	38	Standard endovascular repair	Controlled; small sample size Retrospective analysis Aneurysmal sac embolization with TISSEEL + embolization coils resulted in significantly lower incidence of type II endoleak
Ronsivalle et al.[31]	TISSEEL	Endovascular repair of abdominal aortic aneurysm	Retrospective, nonrandomized, controlled in an Italian center (September 1999–December 2008)	404	Standard endovascular repair	Large sample size Retrospective, nonrandomized Aneurysmal sac embolization with TISSEEL ± embolization coils resulted in significantly lower incidence of type II endoleak
Gorlitzer et al.[25]	TISSEEL	Embolization of type II endoleaks after abdominal aortic aneurysm repair	Retrospective, nonrandomized, uncontrolled in an Austrian center (2001–2007)	17	None	Retrospective, small sample size TISSEEL embolization was effective for sealing type II endoleaks

Continued

TABLE 2
Continued

Citation	Sealant Name	Use	Study Design	Patients, n	Comparator	Study Strengths/ Weaknesses Main Result
Casselman et al.[32]	TISSEEL	Surgical treatment of acute aortic dissection	Retrospective, comparative in a Dutch center (November 1976–February 1999)	121	Reinforcement of aortic root with TISSEEL, Teflon felt, or GRF glue	Retrospective over long period TISSEEL was associated with higher risk of aortic root reoperation
Seguin et al.[33]	TISSEEL	Surgical treatment of acute aortic dissection	Retrospective, uncontrolled in a French center (January 1989–July 1993)	6	None	Retrospective, small sample size TISSEEL in selected cases facilitated surgical repair and had lower mortality rate than aortic arch replacement
Seguin et al.[11]	TISSEEL	Surgical treatment of acute aortic dissection	Retrospective, comparative in a French center (January 1984–July 1990)	42	Aortic stumps reinforced with TISSEEL before implantation of Dacron prosthesis versus intraluminal sutureless graft or Dacron prosthesis sutured to the aorta	Long-term follow-up Retrospective TISSEEL group had significantly less bleeding and lower mortality

GRF, gelatin-resorcinol-formaldehyde; RCT, randomized controlled trial.

facilitated surgery, reduced operative time, and had a lower mortality rate than aortic arch replacement.[33]

Safety in clinical studies

The efficacy data presented above show that the use of fibrin sealants is associated with significant improvements in outcomes in patients with a number of cardiac conditions. Monitoring of safety in randomized clinical trials has not resulted in any reports of treatment-related serious adverse events[7,16,18,19,26,28,30] for sealants that use pooled donor plasma (TISSEEL, Bolheal, Beriplast P, and TachoSil). No known cases of hepatitis infection or HIV seroconversion have been reported.[7,16,34] However, transmission of parvovirus B19 has been linked to contaminated fibrin sealant at a hospital in Japan.[35] Although screening of donor plasma and solvent and vapor treatments may help reduce any possible contamination from parvovirus B19V,[36] there is still a small risk of such infections.[36–38] Two retrospective studies[21,22] have raised the possibility that TISSEEL increases the risk of death in patients undergoing CABG. The potential of fibrin sealants to generate an immunologic response has also been of concern. We discuss here the safety of fibrin sealants using clinical data from controlled and uncontrolled studies.

Thrombosis and mortality risk

In a retrospective report involving data from 2716 patients who had undergone aortocoronary bypass grafting, Lamm et al.[21] used multiple logistic regression to show that TISSEEL was associated with a twofold increase in the risk of a fatal outcome within 30 days of surgery. The authors implicated acute thrombosis of grafts and native coronary arteries in the pathogenesis of these events. In a second retrospective report, Goerler et al.[22] studied data from 2149 patients who had undergone CABG and found that the use of TISSEEL was associated with a 2.2-fold increase in the risk of 30-day mortality after multivariable adjustment for confounding variables.

However, some concerns regarding the conclusions of these retrospective analyses have been raised. Indeed, Cremer[14] pointed out the lack of important information concerning the background hemostatic condition of the patient (before, during, and after CABG) and lack of specific information regarding the indication for fibrin sealant application reduces the ''conclusiveness of these investigations.'' Cremer[14] (and later, Nistor[39]) also mentioned the concerns of cardiovascular surgeons that the method of fibrin sealant application (such as inappropriate spray distance and pressure or improper thawing or misuse intravascularly) may have adversely affected the mortality risk of TISSEEL-treated patients. Moreover, Goerler et al.[22] indicated that the increased mortality risk was contrary to their clinical experience with TISSEEL; they concluded that TISSEEL is ''a safe and effective therapeutic tool in CABG surgery when … applied correctly.''[22] Questions surrounding the risk–benefit ratio of TISSEEL and other fibrin sealants therefore should ideally be examined prospectively in large trials, owing to the limitations of retrospective analyses.

Parallel investigations carried out by the Baxter Vigilance Team and the Paul Ehrlich Institute concluded that there was evidence to support a noncausal

association between TISSEEL and mortality and that the use of TISSEEL was a predictor of mortality rather than a cause.[39] Careful monitoring of safety data from clinical trials and spontaneous safety reports between 2002 and 2008 had revealed no reports of serious adverse events in association with the use of TISSEEL.

Immunologic response

Beriplast P, Bolheal, and TISSEEL contain aprotinin, a naturally occurring bovine protease inhibitor that has been used in surgeries to slow fibrinolysis. In Beriplast P and Bolheal, aprotinin is bovine; TISSEEL contains a synthetic form of aprotinin.[29,36,37,40] Aprotinin, however, has been associated with the potential for hypersensitivity and anaphylactic reactions in humans.[36,41] Although these events are rare and most often seen following intravenous administration of aprotinin in patients with prior exposure,[41] local application of products containing aprotinin can also precipitate an immunologic response after local exposure, and anaphylactic reactions have been reported.[42–44] Per product labeling for TISSEEL[36] in the United States and Beriplast P[37] in Europe, the incidence of hypersensitivity or allergic/anaphylactoid reactions with fibrin sealant is <1 in 10,000 patients. Therefore, history of prior aprotinin exposure is an important consideration for the use of aprotinin-containing products, warranting a careful review of treatment history for a given patient.[36,41] Of note, however, is that such reactions may also occur in patients receiving fibrin sealant for the first time.[36]

COMMENT

Our results are also similar to those reported in a 1996 review by Kjaergard and Fairbrother,[45] which evaluated 24 controlled clinical cardiothoracic studies that used a number of commercially available fibrin sealants and reported that fibrin sealant was successfully used at bleeding sites in reoperations, congenital heart surgery, and type A aortic dissections.[45] Although several randomized controlled trials were found that examined both efficacy and safety of fibrin sealants, particularly TISSEEL, in cardiovascular surgery, many of the trials discussed in this review were small in scale, or were conducted only at a single hospital or center, and many were retrospective. Therefore, there remains a need for large, randomized, controlled, multicenter trials to fully examine the efficacy and safety of these agents, particularly risks of thromboembolism or immunologic reactions.

Blood loss is an inevitable consequence of surgery. Patient outcomes are enhanced by rapid and effective control of bleeding and by achievement of stable, long-term hemostasis. There is evidence that fibrin sealants are effective in controlling bleeding during surgery and are able to achieve rapid hemostasis in situations in which conventional agents have failed.[7,18,26,29,30] The reductions in postoperative blood loss, chest tube drainage volume, and resternotomy rate after cardiac surgery provide circumstantial evidence that the hemostasis achieved by fibrin sealants such as Beriplast P, TISSEEL, and Tachosil is stable throughout the clinically relevant postoperative period.[7,19,23,26] Reducing the use of blood transfusion and blood products, operating theater time,[19,23,26] and the aforementioned effects may reduce surgical costs, but no cost–benefit analyses related to the use of fibrin sealants in cardiovascular surgery have been published to date.

The major concerns surrounding the use of fibrin sealants in cardiac surgery are their potential to induce an immunologic response[42–44] and the apparent association of TISSEEL with increased mortality risk in CABG patients.[21,22] Anaphylactic reactions after repeated use of TISSEEL, Beriplast P, and other aprotinin-containing preparations have been described.[40,42,46,47] The TISSEEL and Beriplast P package inserts contain warnings regarding this possibility and outlines relevant precautions.[36,37] Publications by Lamm et al.[21] and Goerler et al.[22] suggesting an increased risk of mortality with TISSEEL in patients with CABG prompted the introduction of changes to the TISSEEL label, as well as those of other fibrin sealants, aimed at ensuring correct preparation and enforcing the existing warning against intravascular application.[36–38]

CONCLUSIONS

This systematic review summarizes clinical studies and chart review analyses related to the use of fibrin sealants in cardiovascular surgery. Many of the studies evaluated in this review were retrospective analyses with small patient numbers and there were no studies that assessed the pharmacoeconomics of fibrin sealants when used in cardiovascular surgery procedures. Nonetheless, published reports of clinical data on fibrin sealants illustrate improvements in endpoints related to rapidly achieving hemostasis, reducing blood loss, or reducing the number of repeat procedures. Examination of longitudinal chart review safety data revealed some safety events associated with use of TISSEEL (e.g., increased mortality), but no evidence of causality was noted. Overall, fibrin sealants, including TISSEEL, were well tolerated and were effective hemostatic agents in a range of cardiac and aortic surgeries.

Acknowledgments: The author would like to thank Rick Davis, M.S., R.Ph. (Complete Healthcare Communications, Inc., Chadds Ford, PA) and Jane Mannion, M.S. (Baxter Healthcare, Westlake Village, CA) for assistance in the preparation of this manuscript.

REFERENCES

1. Mankad PS, Codiposti M: The role of fibrin sealants in hemostasis. Am J Surg 2001;182:21s–28s.
2. Gibble JW, Ness PM: Fibrin glue: The perfect operative sealant? Transfusion (Paris) 1990;30:741–747.
3. Milne AA: Clinical impact of fibrin sealants. Vox Sang 2004;87:29–30.
4. Borst HG, Haverich A, Walterbusch G, et al: Fibrin adhesive: An important hemostatic adjunct in cardiovascular operations. J Thorac Cardiovasc Surg 1982;84:548–553.

5. Rousou JA, Engelman RM, Breyer RH: Fibrin glue: An effective hemostatic agent for nonsuturable intraoperative bleeding. Ann Thorac Surg 1984;38:409–410.
6. Spotnitz WD, Dalton MS, Baker JW, et al: Reduction of perioperative hemorrhage by anterior mediastinal spray application of fibrin glue during cardiac operations. Ann Thorac Surg 1987;44:529–531.
7. Rousou J, Levitsky S, Gonzalez-Lavin L, et al: Randomized clinical trial of fibrin sealant in patients undergoing resternotomy or reoperation after cardiac operations. A multicenter study. J Thorac Cardiovasc Surg 1989;97: 194–203.
8. Von Oppell UO, Zilla P: Tissue adhesives in cardiovascular surgery. J Long Term Eff Med Implants 1998;8:87–101.
9. Jackson MR, Gillespie DL, Longenecker EG, et al: Hemostatic efficacy of fibrin sealant (human) on expanded poly-tetrafluoroethylene carotid patch angioplasty: A randomized clinical trial. J Vasc Surg 1999;30:461–466.
10. Milne AA, Murphy WG, Reading SJ, et al: Fibrin sealant reduces suture line bleeding during carotid end arterectomy: A randomised trial. Eur J Vasc Endovasc Surg 1995;10:91–94.
11. Seguin JR, Frapier JM, Colson P, et al: Fibrin sealant improves surgical results of type A acute aortic dissections. Ann Thorac Surg 1991;52:745–748.
12. von Segesser LK, Fasnacht MS, Vogt PR, et al: Prevention of residual ventricular septal defects with fibrin sealant. Ann Thorac Surg 1995;60:511–515; discussion 515.
13. Pilon F, Tosato F, Danieli D, et al: Intrasac fibrin glue injection after platinum coils placement: The efficacy of a simple intraoperative procedure in preventing type II endoleak after endovascular aneurysm repair. Interact Cardiovasc Thorac Surg 2010;11:78–82.
14. Cremer J: Fibrin glue in coronary surgery. Eur J Cardiothorac Surg 2007;32:559.
15. Yu L, Gu T, Song L, et al: Fibrin sealant provides superior hemostasis for sternotomy compared with bone wax. Ann Thorac Surg 2012;93:641–644.
16. Lowe J, Luber J, Levitsky S, et al: Evaluation of the topical hemostatic efficacy an safety of TISSEEL VH S/D fibrin sealant compared with currently licensed TISSEEL VH in patients undergoing cardiac surgery: A phase 3, randomized, double-blind clinical study. J Cardiovasc Surg (Torino) 2007;48:323–331.
17. Farhat F, Durand M, Delahaye F, et al: Prosthetic valve sewing-ring sealing with antibiotic and fibrin glue in infective endocarditis. A prospective clinical study. Interact Cardiovasc Thorac Surg 2007;6:16–20.
18. Hanks JB, Kjaergard HK, Hollingsbee DA: A comparison of the haemostatic effect of Vivostat patient-derived fibrin sealant with oxidised cellulose (Surgicel) in multiple surgical procedures. Eur Surg Res 2003;35:439–444.
19. Codispoti M, Mankad PS: Significant merits of a fibrin sealant in the presence of coagulopathy following paediatric cardiac surgery: Randomised controlled trial. Eur J Cardiothorac Surg 2002;22:200–205.
20. Leca F, Karam J, Vouhe PR, et al: Surgical treatment of multiple ventricular septal defects using a biologic glue. J Thorac Cardiovasc Surg 1994;107:96–102.
21. Lamm P, Adelhard K, Juchem G, et al: Fibrin glue in coronary artery bypass grafting operations: Casting out the devil with Beelzebub? Eur J Cardiothorac Surg 2007;32:567–572.
22. Goerler H, Oppelt P, Abel U, et al: Safety of the use of Tissucol© Duo S in cardiovascular surgery: Retrospective analysis of 2149 patients after coronary artery bypass grafting. Eur J Cardiothorac Surg 2007;32:560–566.
23. Kieser TM, Maitland A, Parsons L, et al: Reduced postoperative bleeding following use of TISSEEL fibrin sealant in 300 patients undergoing open-heart surgery. In: Wolner E, Schlag GO, Eckersberger F (eds). Cardiovascular Surgery: Thoracic Surgery. Vol 6. Springer-Verlag, Berlin, Heidelberg, New York, 1995, pp. 43–54.
24. Huth C, Seybold-Epting W, Hoffmeister HE: Local hemostasis with fibrin glue after intracardiac repair of tetralogy of Fallot and transposition of the great arteries. Thorac Cardiovasc Surg 1983;31:142–146.
25. Gorlitzer M, Mertikian G, Tmka H, et al: Translumbar treatment of type II endoleaks after endovascular repair of abdominal aortic aneurysm. Interact Cardiovasc Thorac Surg 2008;7:781–784.
26. Bajardi G, Pecoraro F, Mirabella D: Efficacy of TachoSil patches in controlling Dacron suture-hole bleeding after abdominal aortic aneurysm open repair. J Cardiothorac Surg 2009;4:60.
27. Zanchetta M, Faresin F, Pedon L, et al: Intraoperative intrasac thrombin injection to prevent type II endoleak after endovascular abdominal aortic aneurysm repair. J Endovasc Ther 2007;14:176–183.
28. Christenson JT, Kalangos A: Autologous fibrin glue reinforced by platelets in surgery of ascending aorta. Thorac Cardiovasc Surg 2004;52:225–229.
29. Minato N, Katayama Y, Yunoki J, et al: Hemostatic effectiveness of a new application method for fibrin glue, the ''rub-and-spray method'', in emergency aortic surgery for acute aortic dissection. Ann Thorac Cardiovasc Surg 2009;15:265–271.
30. Maisano F, Kjaergard HK, Bauernschmitt R, et al: TachoSil surgical patch versus conventional haemostatic fleece material for control of bleeding in cardiovascular surgery: A randomised controlled trial. Eur J Cardiothorac Surg 2009;36:708–714.
31. Ronsivalle S, Faresin F, Franz F, et al: Aneurysm sac ''thrombization'' and stabilization in EVAR: A technique to reduce the risk of type II endoleak. J Endovasc Ther 2010;17:517–524.
32. Casselman FP, Tan ES, Vermeulen FE, et al: Durability of aortic valve preservation and root reconstruction in acute type A aortic dissection. Ann Thorac Surg 2000;70:1227–1233.
33. Seguin JR, Picard E, Frapier JM, et al: Repair of the aortic arch with fibrin glue in type A aortic dissection. J Card Surg 1994;9:734–738; discussion 738–739.
34. Joch C: The safety of fibrin sealants. Cardiovasc Surg 2003;11:23–28.
35. Hino M, Ishiko O, Honda KI, et al: Transmission of symptomatic parvovirus B19 infection by fibrin sealant used during surgery. Br J Haematol 2000;108:194–195.
36. TISSEEL (fibrin sealant). Full Prescribing Information. Baxter Healthcare Corporation, Westlake Village, CA, 2012.
37. Beriplast P COMBI-SET (fibrin sealant). Full Prescribing Information. CSL Behring, Marburg, Germany, 2008.
38. TachoSil (fibrin sealant). Full Prescribing Information. Nycomed Austria GmbH, Linz, Austria, 2009.
39. Nistor RF: Fibrin sealant in coronary artery bypass grafting surgery; reflection on risk and benefit. Eur J Cardiothorac Surg 2008;33:317.
40. Taylor LM Jr, Mueller-Velten G, Koslow A, et al: Prospective randomized multicenter trial of fibrin sealant versus thrombin-soaked gelatin sponge for suture- or needle-hole bleeding from polytetrafluoroethylene femoral artery grafts. J Vasc Surg 2003;38:766–771.

41. Beierlein W, Scheule AM, Dietrich W, et al: Forty years of clinical aprotinin use: A review of 124 hypersensitivity reactions. Ann Thorac Surg 2005;79:741–748.
42. Scheule AM, Beierlein W, Arnold S, et al: The significance of preformed aprotinin-specific antibodies in cardiosurgical patients. Anesth Analg 2000;90:262–266.
43. Scheule AM, Beierlein W, Wendel HP, et al: Fibrin sealant, aprotinin, and immune response in children undergoing operations for congenital heart disease. J Thorac Cardiovasc Surg 1998;115:883–889.
44. Scheule AM, Beierlein W, Wendel HP, et al: Aprotinin in fibrin tissue adhesives induces specific antibody response and increases antibody response of high-dose intravenous application. J Thorac Cardiovasc Surg 1999;118: 348–353.
45. Kjaergard HK, Fairbrother JE: Controlled clinical studies of fibrin sealant in cardiothoracic surgery—A review. Eur J Cardiothorac Surg 1996;10:727–733.
46. Kober BJ, Scheule AM, Voth V, et al: Anaphylactic reaction after systemic application of aprotinin triggered by aprotinin-containing fibrin sealant. Anesth Analg 2008; 107:406–409.
47. Shirai T, Shimota H, Chida K, et al: Anaphylaxis to aprotinin in fibrin sealant. Intern Med 2005;44:1088–1089.