Use of Sealants in Pancreatic Surgery: Critical Appraisal of the Literature

Abe Fingerhut^{a, c} Nicolas Veyrie^b Toufik Ata^a Nicholas Alexakis^c
Emmanuel Leandros^c

^aDepartment of Digestive Surgery, Centre Hospitalier Intercommunal, Poissy, and ^bDepartment of Digestive Surgery, Hôtel-Dieu, Université Paris Descartes, AP-HP, Paris, France; ^cDepartment of Surgery, University of Athens, Hippokration Hospital, Athens, Greece

Key Words

Fibrin sealants • Pancreatic resection • Fistula

Abstract

Background/Aims: Fibrin sealants containing both fibrin and thrombin have been used to control bleeding, reinforce suture lines and enhance tissue healing. However, the literature provides contradictory results. **Methods:** A systematic literature search was performed to determine the use of fibrin sealants in pancreatic surgery. These articles were then critically appraised according to their methodologies, outcomes and conclusions. **Results:** Twenty-four studies were found, including 6 controlled randomized trials. Of these, 16 studies were analyzed. Many methodological flaws and lack of consistency in definitions were found, making comparisons between studies difficult if not impossible. **Conclusion:** Because of the heterogeneity and lack of high-level evidence, the current literature does not allow us any conclusion: neither is there proof that fibrin sealants are of any real utility in pancreatic surgery, nor that they do not work. Further large-scale controlled trials are necessary before concluding that they do or do not provide any advantages in pancreatic surgery.

Copyright © 2009 S. Karger AG, Basel

Fibrin sealants have proved successful in controlling bleeding, providing reinforcement of suture lines and enhancing tissue sealing and may also be used to vehicle drugs such as antibiotics [1] and perhaps someday chemotherapy. Most publications on fibrin sealants have dealt with their use in the prevention or the limitation of autologous blood loss [1, 2] and have involved cardiovascular, orthopedic, thoracic, hepatic, pulmonary as well as orthodontic surgery [3, 4] and, more recently, colonic and gastroenteric anastomoses in bariatric surgery [5]. In pancreatic surgery, sealants have most often been used with the intent to prevent pancreatic fistula after pancreatic surgery, as early as 1978 [6]. Since that date, fibrin sealants have been the object of reports concerning management of trauma and resections of the head [7, 8] and the tail [9], as well as treatment of low-output pancreatic fistula [10].

Although several experimental studies [11–14] seem to indicate that a fibrin sealant is beneficial, improving the fistula rate in various settings (trauma, resection, transplantation), the outcomes and conclusions of clinical

Large excerpts of this paper were part of an oral presentation during the 8th World Congress of the International Hepato-Pancreato-Biliary Association meeting held in Mumbai, India, February 27, 2008. A.F. has been a consultant for Nycomed Pharma.

Table 1. Levels of evidence, according to Cook et al. [17]

I	Randomized trials with low false-positive and low false-negative errors (high power) Meta-analysis of multiple well-designed, controlled studies
II	At least 1 well-designed experimental study; randomized trials with high false-positive or high false-negative errors or both (low power)
III	Well-designed, quasi-experimental studies, such as nonrandomized, controlled, single-group, preoperative-postoperative comparison, cohort, time or matched case-control series
IV	Well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V	Case reports and clinical examples

studies are contradictory. For these reasons, we decided to review the literature on the use of fibrin sealants in pancreatic surgery, with critical appraisal.

Methods

A systematic search of the electronic literature was performed using the Medline, Embase and the Cochrane Central Register of Controlled Trials for the years 1983–2008 to obtain access to all publications, especially randomized controlled trials, systematic reviews and meta-analyses involving the use of fibrin sealant in pancreatic surgery.

The search strategy was that described by Dickersin et al. [15] and Tumber and Dickersin [16] with the appropriate specific search terms. These included: fibrin glue, fibrin sealant, sealant, fistula, anastomotic leaks, duct, duct occlusion and controlled trials. The level of evidence was made according to Cook et al. [17] (table 1).

Results

Twenty-four studies were found, including 6 controlled randomized trials. Of these, 16 studies were analyzed in detail and critically appraised, of which 10 are summarized in table 2. Studies concerned either the use of fibrin sealants to reinforce pancreatic anastomoses or stump closures, or to occlude the main pancreatic duct.

Use of Fibrin Sealants to Reinforce Pancreatic Anastomoses or Stump Closure

One of the very first case series was reported in 1986 involving patients operated on in 1978 [6]. Fibrin glue (Tissucol®, Immuno, Vienna, Austria) was used in all

cases, heralding promising perspectives. Kram et al. [8] used fibrin sealant applied directly to penetrating pancreatic injuries, pancreatic suture and staple lines in patients treated by partial resection, as well as pancreatico-intestinal anastomoses, including 10 patients with trauma and 5 with benign nontraumatic pancreatic pathology. Postoperatively, none of the patients developed pancreatic fistulas, abscesses or pseudocysts. The level of evidence for these 2 studies is 4.

Tashiro et al. [18] compared the outcome [19] of pancreaticojejunostomy in 112 patients: 42 with (group I) and 70 without (group II) fibrin sealant-reinforced pancreaticoenteric anastomosis. Although only 1 patient in group I (vs. 2 patients in group II) had a minor leak, there were no major leaks or operative deaths in group I (vs. 1 major leak resulting in death in the second group). The authors recommended using the biological adhesive system for prevention of anastomotic leakage after pancreaticojejunostomy especially when the pancreatic parenchyma was healthy. The level of evidence is 3.

Suzuki et al. [19] evaluated the use of fibrin sealant on the pancreatic stump after distal pancreatectomy for the prevention of postoperative pancreatic fistula in a prospective, randomized clinical trial. Twenty-six of 56 patients who underwent distal pancreatectomy for gastric cancer or pancreatic disease were randomly assigned to have fibrin sealant applied to the suture line of the pancreatic stump after ligation of the main pancreatic duct and fish-mouth closure of the pancreatic stump; 30 had just closure, without fibrin sealant (control group). Pancreatic fistula was defined as a pancreatic fluid discharge for over 7 postoperative days with an amylase concentration more than 3 times the serum amylase concentration. The overall incidence of pancreatic fistula was 28.6%. Postoperative pancreatic fistulas occurred in 4 patients (15.4%) in the fibrin sealant group and in 12 patients (40.0%) in the control group ($p = 0.04$). The lower pancreatic fistula rate was seen in the fibrin sealant group also when analyzing patients with gastric cancer or pancreatic disease only, although the difference was not statistically significant. The authors recommended the use of fibrin sealant as a complement to other prophylactic methods.

The study by d'Andrea et al. [20] was a prospective randomized study including 97 patients. Of these, 46 had pancreatic inflammatory diseases while 51 had pancreatic or peripancreatic tumors. Surgical treatment included 30 pancreatoduodenectomies, 40 pancreaticojejunostomies, 23 left pancreatic resections and 4 tumor excisions. Forty-three patients were randomized to intraop-

Table 2. List of major studies with use of fibrin sealant to decrease the complication (fistula) rate after pancreatic resection, trauma or transplantation

Study	Methods	Patients	Interventions	Outcomes
Tashiro et al. [18], 1987	randomized but retrospective and incomplete analysis	group I: n = 42 group II: n = 70	FG in PJ anastomosis no FG in PJ	major leak death: n = 0 minor leak: n = 1 major leak/death: n = 1 minor leak: n = 2
Lorenz et al. [28], 1988	comparative, nonrandomized	group 1: n = 40 group 2: n = 40	FG in MPD during PD no FG	no protective effect
Kram et al. [8], 1991	nonrandomized	n = 15 (variety of conditions)	FG	no fistula, abscess
Cavallini et al. [7], 1991	nonrandomized	n = 6 (PD)	FS on pancreatic stump	5 with fistula, 1 with abscess
D'Andrea et al. [20], 1994	randomized	group 1: n = 43 group 2: n = 54 (variety of conditions and resections)	FS no FS	PF: n = 6 (13.9%) PF: n = 6 (11.1%)
Suzuki et al. [19], 1995	randomized	group 1: n = 26 group 2: n = 30	FG on stump after DP no FG	PF: n = 4 (15.4%) PF: n = 12 (40%) (p = 0.04)
Tran et al. [30], 2002	randomized	group 1: n = 83 group 2: n = 86	PJ anastomosis after PD no anastomosis + FS in MPD	no difference in number of complications (p = 0.69)
Suc et al. [29], 2003	randomized	group 1: n = 102 group 2: n = 80	FG in MPD after PD/ DP no FG	no difference in PF/intra-abdominal complications (p < 0.2)
Lillemoe et al. [21], 2004	randomized	group 1: n = 59 (PD) group 2: n = 66 (PD)	FG to PJ anastomosis no FG	PF 26% PF 30%
Velanovich [9], 2007	comparative, nonrandomized	group 1: n = 8 (lap DP) group 2: n = 13 (lap DP)	FS on stump after DP no FS	PF: n = 0 PF: n = 3

FG = Fibrin sealant; PJ = pancreaticojejunostomy; MPD = main pancreatic duct; DP = distal pancreatectomy; FS = fibrin sealant; PF = pancreatic fistula; lap = laparoscopic.

erative sealing of the anastomosis with fibrin sealant, while the 54 remaining patients had no fibrin sealing during surgery. Six patients in each group developed a pancreatic fistula (13.9 vs. 11.1%); this difference was not found to be statistically significant. The level of evidence for both of these studies [19, 20] is 2.

Lillemoe et al. [21] conducted a randomized controlled trial published in 2004 evaluating the role of fibrin sealant reinforcement of pancreatic anastomoses as an adjunctive measure to decrease the rate of pancreatic fistula after high-risk pancreatoduodenectomy. After completion of the pancreaticojejunal anastomosis, the patients were randomized to topical application of fibrin sealant to the surface of the anastomosis or no such application. The primary postoperative end points in this

study were pancreatic fistula, total complications, death and duration of hospital stay. Fifty-nine patients were randomized to receive 8 ml of rapid-acting fibrin sealant applied circumferentially to the entire pancreaticojejunostomy anastomotic site after completion of all 3 anastomoses. In the control arm, 66 patients did not receive fibrin sealant application. The overall incidence of pancreatic fistula was 28% (35 of 124 patients) with no statistically significant difference found between the fibrin sealant group at 26% (15 of 58 patients) and the control group at 30% (20 of 61 patients). Further, there were no statistically significant differences found with respect to total or specific complications such as postoperative bleeding, infection or delayed gastric emptying, mortality rates (1 death in the control group), mean duration of

postoperative stay (fibrin sealant 12.2 days, control 13.6 days) or mean duration of stay for patients in whom pancreatic fistula developed (fibrin sealant 18.9 days vs. control 21.7 days). This study was interrupted after intermediate analysis of 124 patients. The level of evidence is 2.

In the distal pancreas, Kleeff et al. [22] looked at the risk factors for fistula in 302 consecutive patients undergoing operation during a 13.5-year period in 2 hospitals by the same team.

Patients were divided into 4 groups according to how the pancreatic stump was closed. An unknown number of some 240 patients had reinforcement of the closure by a fibrinogen/thrombin-coated collagen patch (Tachosil®, Nycomed Pharma, Copenhagen, Denmark). The level of evidence is 4.

These results contrast with an older, but smaller, level 2 randomized study from Bassi et al. [23] in which 69 consecutive patients were randomized to stump closure with simple suture closure of the stump (plus ligation of the main pancreatic duct; $n = 15$), suture closure plus ligation reinforced with fibrin sealant ($n = 11$), suture closure plus ligation reinforced with polypropylene mesh ($n = 15$), pancreaticojejunostomy ($n = 14$), or suture closure with a stapler ($n = 14$). No statistically significant difference in the complication or fistula rate was found between any of the 5 groups, the latter ranging from 7% in the pancreaticojejunostomy group to 33% in the group of simple closure plus ligation (27% in the fibrin sealant group).

Ohwada et al. [24] conducted a nonrandomized clinical level 3 cohort study in 111 patients comparing fibrin sealant, simple or combined with the sandwich technique, to prevent pancreatic fistula following distal pancreatectomy. Morbidity was 21.8% for the patients in the combined fibrin + sandwich group versus 33.9% in the sealant alone group.

Velanovich [9] reported the use of fibrin sealant in laparoscopic or hand-assisted distal pancreatectomy in 8 cases with 5 ml of fibrin sealant (Tisseal, Baxter Healthcare, Deerfield, Ill., USA) applied to the cut edge of the pancreatic remnant. Omentum, which had been dissected to expose the raw surface, was then applied over the pancreatic remnant and fastened to the cut edge by the fibrin sealant. Pancreatic fistula was defined as any amylase-rich fluid found in the drain (placed routinely) or any juxtaposed fluid collection next to the pancreatic remnant found by routine computed tomography scans performed on postoperative day 3. In this level 4 study, these 8 patients were historically compared with the previous 13 patients who underwent laparoscopic distal pan-

createctomy without fibrin sealant. No patients in the fibrin sealant group experienced pancreatic fistula, as compared with 3 patients (23%) in the no sealant group.

Occlusion of the Main Pancreatic Duct by Injection of Fibrin Sealant

Among the nonrandomized or uncontrolled studies reported, no postoperative pancreatic fistulas were observed in 80 [25] and 12 [26] patients undergoing pancreatoduodenectomy for carcinoma or for chronic pancreatitis, respectively, followed by immediate pancreatodigestive anastomosis. Marczell and Stierer [27] injected fibrin sealant into the main pancreatic duct, completed by ductal ligation, with the intention of avoiding an anastomosis between the pancreas and the intestinal tract in 44 patients; only 3 patients had a postoperative complication. Cavallini et al. [7] used fibrin sealant to occlude the residual pancreatic stump in 6 consecutive patients with resectable periampullary carcinoma. While pancreatic fistula developed in 5 cases, all resolved spontaneously in 1–4 months. The 6th patient developed an intra-abdominal collection which required a CT-guided percutaneous aspiration 3 months after operation. Pancreatic endocrine function was assessed in 5 patients at 3 months after operation, and glucose metabolism was found to be normal in all. The authors concluded that fibrin sealant injection was a safe and satisfactory method to control the exocrine secretion, particularly indicated in the case of a healthy, nonfibrotic pancreatic stump, at high risk of anastomotic fistula. The level of evidence for these 4 studies [7, 25–27] is 4.

On the other hand, in a prospective, comparative, but nonrandomized level of evidence 3 trial of 80 patients undergoing pancreatoduodenectomy (40 for cancer and 40 for chronic pancreatitis), half of each group having either ductal occlusion with fibrin sealant or not [28], no significant protective effect was afforded by the injection of glue. Moreover, among the 40 patients with cancer, there were twice as many complications in patients who underwent ductal occlusion as compared with those who did not ($p = 0.2$).

Two controlled level 1 randomized trials employing fibrin sealant to occlude the main pancreatic duct have been performed [29, 30]. Suc et al. [29] tested the effects of ductal occlusion with fibrin sealant (Tissucol) by comparing 102 patients with duct occlusion with fibrin sealant with 80 patients without. The 2 groups were similar concerning the proportions of patients undergoing pancreaticojejunostomy versus pancreaticogastrostomy, or the type of stump closure when distal pancreatectomy

was performed. However, they did differ in that more patients in the fibrin occlusion group had fibrin-reinforced anastomosis, octreotide prophylaxis and fibrotic pancreas, all factors which could have obscured the positive effects of fibrin sealant occlusion, but overall, and after adjustment for the 3 above-mentioned risk factors, there was no statistically significant difference found between the 2 groups concerning the rate of patients with intraoperative abdominal complications, notably pancreatic fistulas or their severity, after pancreatic resection. Tran et al. [30] ran a trial comparing pancreaticojejunostomy in 1 arm with no anastomosis but with occlusion of the main pancreatic duct in the other, the occluding agent used being injection of Ethibloc (n = 18), Neoprene (n = 45) or Tissucol (n = 23), the latter in combination with aprotinin (Trasylol). While no overall benefit could be shown in favor of one or the other technique, subgroup analysis did not show any statistically significant differences in outcomes between the 3 chemical substances used for occlusion, but there were 5 cases of sepsis and bleeding from pancreatitis with subsequent leakage encountered in the Ethibloc group, which led to a high mortality rate in this group of patients in Rotterdam. Moreover, endocrine insufficiency was observed statistically significantly more often in the duct occlusion group.

Discussion

While all fibrin sealants contain both fibrinogen and thrombin, they differ in their final composition, and by consequence, in the properties of the resulting fibrin clot. This may influence their use in different surgical procedures: stronger clots are obtained with high concentrations of fibrinogen, while sealants containing higher concentrations of thrombin produce clots more rapidly, an advantage when initial and rapid hemostasis limits or stops blood loss. On the other hand, when precise tissue approximation is the goal (e.g., a skin flap), a slower clot formation is desirable. Some sealants are supplemented with factor XIII which may increase the tensile strength and stability of the clot and improve hemostasis. Antifibrinolytic agents (e.g., aprotinin and aminocaproic acid) increase the duration of the clot by inhibiting fibrinolysis, but have recently been shown to be unnecessary [31]. However, fibrin sealants containing aprotinin may have an added advantage when used on surgical sites with naturally high concentrations of fibrinolytic agents, such as the pancreas.

The physical properties of the fibrin sealants also vary. For example, the fibrinogen component is relatively viscous and requires much force to inject it through a long catheter. Fibrin sealants with a fibrinogen component of low viscosity are easier to use than highly viscous solutions where the sealant is applied through a catheter.

Until recently, the use of fibrin sealants in the United States has been limited to noncommercial products – ‘homebrews’. Blood bank-derived fibrin sealants, autologous and point-of-use prepared sealants may vary in their composition (fibrinogen and thrombin concentrations as well as the adjunction of antifibrinolytic agents) from one preparation to the next, and hence, be less predictable in their performance [32]. Because of such variation in the mechanical clot strength, the clotting rate, viscosity, adhesiveness and resistance to proteolysis, handling and application are difficult. Fibrin sealants are available as liquids and sprays, while the Tachosil (Nycomed) sponge combines fibrin and thrombin with collagen (table 3).

Critical Appraisal of the Literature

Fibrin Sealant as an Adjunct to Anastomosis

All in all, there were 3 case series, 1 cohort, 1 poorly randomized and 4 controlled randomized studies to consider.

The study by Cavallini et al. [7] was a case series of 6 patients. The study by Kram et al. [8] was also not controlled, and the authors’ recommendation to use fibrin sealant to seal off pancreatic injuries, resections and anastomoses as a potential aid in preventing fistulas after pancreatic surgery, sealing of pancreatic biopsy sites and occlusion of the pancreatic duct in pancreatic transplantation was at best speculative.

In the study by Kleeff et al. [22], the exact number of patients with fibrin sealant in each group was not known, so it is impossible to determine the exact role played by fibrin sealant. In the meta-analysis of techniques of closure from the same team [33], the same shortcomings of many of the trials analyzed herein were confirmed.

The study by Tashiro et al. [18] cannot be considered a truly randomized controlled study because only 22 patients in group I and 26 patients in group II (of a total of 112 patients entered into the study) were reviewed for outcome, and this was done retrospectively.

Two small truly randomized studies produced contradictory results. The study by Suzuki et al. [19] (including 56 patients) showed that the overall incidence of postop-

Table 3. List of commercially available fibrin sealants

Manufacturer	Component	Brand name
Baxter International Inc.	human thrombin-factor XIII-fibrinogen	Tisseel (USA, Europe), also appears as Tissusol
Baxter International Inc.	gelatin matrix thrombin	FloSeal (USA)
Ethicon	human thrombin-fibrinogen	Evicel (USA)
Nycomed Pharma	human thrombin-fibrinogen + collagen	TachoSil (Europe)
CSL Behring	human thrombin-factor XIII-fibrinogen	Barillas P (Europe)
King Pharmaceuticals	bovine thrombin	Thrombin-JMI (USA)
Omrix Biopharmaceuticals S.A. – Ethicon	human thrombin-factor XIII-fibrinogen	Quixil (Europe)

erative pancreatic fistula was reduced to 15% with the use of fibrin sealant (compared with 40% in the control group; $p = 0.04$). The overall incidence of pancreatic fistula was 29%, but pancreatic fistula was defined as a pancreatic fluid discharge for over 7 postoperative days with an amylase concentration more than 3 times the serum amylase concentration, a sufficiently general definition, so that even a small pancreatic leakage could be diagnosed. The study by d'Andrea et al. [20] did not find any statistically significant difference in outcome. However, in this latter study, the randomization process was not described, and even if the authors stated that there was no difference in the fistula rate when patients were analyzed according to the pathology or type of pancreatic resection, the numbers for this subgroup analysis were too small to be of any value.

The study by Lillemoe et al. [21] has several methodological shortcomings: first of all, although fistula was used to calculate the number of patients necessary to obtain the power of 80%, the results provided (26% in the fibrin group vs. 30% in the control group) corresponded to the number of patients with 1 or more complications, not to the fistula rate. Second, looking at fistula only, there were 8/58 (14%) patients with pancreatic fistula in the fibrin group versus 16/66 (24%) in the control group, indicating a much higher rate than reported in other studies originating from the same group. If the present study had been continued with the same fistula rate until reaching the number of patients necessary, there would have been 15/112 versus 27/112 patients, practically a 2-fold increase, and the p value would have been 0.06, nearly statistically significant. However, if the number of fistulas was one less in each group, 14 and 26, respectively, the p value would have been 0.027! This seems to indicate that the authors interrupted this study prematurely. In fact, and this is the third methodological criticism, nowhere in this paper do we find the calculation that al-

lowed the authors to state that if they continued the study, it was impossible to obtain a statistically sound positive (or negative) result [34]. Last, the authors stated that an 'informal' data safety and monitoring board reviewed the adverse events only once per year. Formal data safety and monitoring boards should be an integral part of randomized controlled studies and should meet regularly [35].

In the study by Bassi et al. [23], the 27% fistula rate found in the 11 patients with simple closure plus ligation and fibrin sealant was not statistically significantly different from any of the other 4 groups, but obviously, the numbers of patients in each group were quite small, and as the number of patients necessary was not mentioned, the β error may have been large. Moreover, the randomization procedure was not detailed, and we do not know how many patients in each group had soft versus hard parenchyma.

The nonrandomized clinical cohort study by Ohwada et al. [24] including 111 patients cannot be used to prove that fibrin does or does not work, as both groups of patients had fibrin sealant.

The study by Velanovich [9] was a historical comparison of a series of 8 patients with fibrin sealant applied to the pancreatic stump after undergoing laparoscopic distal pancreatectomy (vs. 13 previously operated patients without fibrin sealant), a study that has to be classed level 3.

Injection of Fibrin Sealant into the Main Pancreatic Duct

Suggested as a means of reducing exocrine pancreatic secretion and thus decreasing the risk of fistula experimentally [36], ductal occlusion has been reported previously with [25, 26, 28] or without [7, 37–39] associated anastomosis. Ductal occlusion with neoprene or prolamine, both nonresorbable glues, used most often without anastomosis after pancreatoduodenectomy [39], has been

abandoned because permanent occlusion induces pancreatic atrophy and complete loss of exocrine function [32]. The rationale to use resorbable glues [6, 7, 26, 27, 40] was to limit the action of pancreatic proteases while waiting for the pancreatodigestive tract anastomosis or the pancreatic stump to heal after (proximal or distal, respectively) pancreatectomy. With the intention of increasing its efficacy, aprotinin, which should theoretically delay the enzymatic dissolution of the glue, was added [31].

Contrasting with the results of the nonrandomized or uncontrolled studies, i.e. no postoperative pancreatic fistulas observed in 80 [25] and 12 [26] patients undergoing pancreatoduodenectomy, or the case series of Marczell et al. [27] (3 postoperative complications), no significant protective effect was afforded by the injection of glue in the prospective, comparative, but nonrandomized trial of Lorenz et al. [28]. Of the 2 level 1 controlled randomized trials employing fibrin sealant to occlude the main pancreatic duct, neither Suc et al. [29] nor Tran et al. [30] were able to demonstrate any overall benefit.

Failure of fibrin sealant ductal occlusion to act on the pancreatic fistula rate can be explained in several ways: (1) blockage of the main pancreatic duct, even transient, might artificially increase the secretion of pancreatic juice in the severed secondary canals [24] or on the suture line; (2) occlusion of the main pancreatic duct might be incomplete [41] or insufficient in human beings. Experimentally, sealant absorption is inversely proportional to the concentration of aprotinin. In the study by Suc et al. [29], 10,000 kallikrein inhibitor units/ml of aprotinin was used, which might not have been high enough to be effective. Both Waclawiczek and Boeckl [25] and Cavallini et al. [7] advocated using at least 20,000 kallikrein inhibitor units/ml. However, in these 2 retrospective studies, whereas no fistulas were observed in the 80 cases of the former study, 5 of 6 patients in the latter still developed

fistulas. Therefore, the effectiveness of higher doses of aprotinin in order to maintain occlusion for more than 8 days remains to be tested.

One further criticism of all these studies is that no uniform, standardized definition of pancreatic fistula was used, making comparisons between them very difficult, if not impossible. It is for this reason that the International Study Group on Pancreatic Fistula Definition, composed of 38 surgeons from 9 different countries, met to concur with each other and publish a standardized, workable definition of postoperative pancreatic fistula which should be used in the future for all trials in which such comparisons are made [23].

In conclusion, the use of fibrin sealant to reinforce the pancreatoenteric anastomosis has not yet been proven to be effective, but because of the small numbers in some studies, or the noncontrolled or doubtful methodology in others, no conclusions can be drawn as to whether fibrin sealant is useful or not [42]. Certainly large, nonbiased randomized trials are necessary in this domain.

On the other hand, injection of fibrin sealant into the main pancreatic duct, associated with pancreatoenteric anastomosis or not, has not been shown to be effective in reducing the complication rate, and notably, the rate of fistulas.

However, open questions remain: (1) can the composition (of fibrin and thrombin, on the one hand, and aprotinin, on the other) be changed in order to improve the efficacy; (2) will the adjunction of other material, such as collagen, be of any added value. The FRENCH (fédération de recherche en chirurgie) is currently undertaking a large controlled randomized study to determine whether the Tachosil (fibrin + thrombin + collagen) sponge, wrapped around the pancreatoenteric anastomosis or the pancreatic stump, can help prevent pancreatic fistula after distal pancreatectomy.

References

- 1 Carless PA, Anthony DM, Henry DA: Systematic review of the use of fibrin sealant to minimize perioperative allogeneic blood transfusion. *Br J Surg* 2002;89:695–703.
- 2 Martinowitz U, Saltz R: Fibrin sealant. *Curr Opin Hematol* 1996;3:395–402.
- 3 Belboul A, Dernevik L, Aljassim O, Skrbic B, Radberg G, Roberts D: The effect of autologous fibrin sealant (Vivostat) on morbidity after pulmonary lobectomy: a prospective randomised, blinded study. *Eur J Cardiothorac Surg* 2004;26:1187–1191.
- 4 Schwartz M, Madariaga J, Hirose R, Shaver TR, Sher L, Chari R, Colonna JO 2nd, Heaton N, Mirza D, Adams R, Rees M, Lloyd D: Comparison of a new fibrin sealant with standard topical hemostatic agents. *Arch Surg* 2004;139:1148–1154.
- 5 Silecchia G, Boru CE, Mouiel J, Rossi M, Anselmino M, Tacchino RM, Foco M, Gaspari AL, Gentileschi P, Morino M, Toppino M, Basso N: Clinical evaluation of fibrin glue in the prevention of anastomotic leak and internal hernia after laparoscopic gastric bypass: preliminary results of a prospective, randomized multicenter trial. *Obes Surg* 2006;16:125–131.
- 6 Waclawiczek HW, Boeckl O: Clinical experience with fibrin gluing in general and thoracic surgery. *Zentralbl Chir* 1986;111:16–24.
- 7 Cavallini M, Talerini A, Stipa F: Occlusion of the duct with a fibrin glue and preservation of the pylorus after resection of the duodenum and head of the pancreas for periampullary carcinoma. *Minerva Chir* 1991;46:733–739.

- 8 Kram HB, Clark SR, Ocampo HP, Yamaguchi MA, Shoemaker WC: Fibrin glue sealing of pancreatic injuries, resections, and anastomoses. *Am J Surg* 1991;161:479–481; discussion 482.
- 9 Velanovich V: The use of tissue sealant to prevent fistula formation after laparoscopic distal pancreatectomy. *Surg Endosc* 2007;21:1222.
- 10 Cothren CC, McIntyre RC Jr, Johnson S, Stiegmann GV: Management of low-output pancreatic fistulas with fibrin glue. *Am J Surg* 2004;188:89–91.
- 11 Balcom JH 4th, Keck T, Warshaw AL, Graeme-Cook F, Fernandez-del Castillo C: Prevention of pancreatic fistula with a new synthetic, absorbable sealant: evaluation in a dog model. *J Am Coll Surg* 2002;195:490–496.
- 12 Hauser CJ: Hemostasis of solid viscus trauma by intraparenchymal injection of fibrin glue. *Arch Surg* 1989;124:291–293.
- 13 Houvenaeghel G, Orsoni P, Delpero JR, Monges G, Picaud R, Guerin G: Obstruction of pancreatic ducts with a fibrin glue. Study after segmentary autotransplantation in dogs. *J Chir (Paris)* 1991;128:94–98.
- 14 Stojanovic M, Jeremic M, Stojanovic P, Stojiljkovic M, Gmijovic D, Stanojkovic Z, Savic V, Djordjevic V, Cvetkovic Z, Kostov M, Colovic R: Use of fibrin glue in the prevention of leakage in pancreatico-jejunal anastomoses. *Acta Chir Iugosl* 2002;49:39–45.
- 15 Dickersin K, Scherer R, Lefebvre C: Identifying relevant studies for systematic reviews. *BMJ* 1994;309:1286–1291.
- 16 Tumber MB, Dickersin K: Publication of clinical trials: accountability and accessibility. *J Intern Med* 2004;256:271–283.
- 17 Cook DJ, Guyatt GH, Laupacis A, Sackett DL: Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1992;102:305S–311S.
- 18 Tashiro S, Murata E, Hiraoka T, Nakakuma K, Watanabe E, Miyauchi Y: New technique for pancreaticojejunostomy using a biological adhesive. *Br J Surg* 1987;74:392–394.
- 19 Suzuki Y, Kuroda Y, Morita A, Fujino Y, Tanioka Y, Kawamura T, Saitoh Y: Fibrin glue sealing for the prevention of pancreatic fistulas following distal pancreatectomy. *Arch Surg* 1995;130:952–955.
- 20 D'Andrea AA, Costantino V, Sperti C, Pedrazzoli S: Human fibrin sealant in pancreatic surgery: it is useful in preventing fistulas? A prospective randomized study. *Ital J Gastroenterol* 1994;26:283–286.
- 21 Lillemoe KD, Cameron JL, Kim MP, Campbell KA, Sauter PK, Coleman JA, Yeo CJ: Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy? Results of a prospective randomized trial. *J Gastrointest Surg* 2004;8:766–772; discussion 772–774.
- 22 Kleeff J, Diener MK, Z'Graggen K, Hinz U, Wagner M, Bachmann J, Zehetner J, Muller MW, Friess H, Buchler MW: Distal pancreatectomy: risk factors for surgical failure in 302 consecutive cases. *Ann Surg* 2007;245:573–582.
- 23 Bassi C, Butturini G, Falconi M, Salvia RNS, Caldiron E, Talamini G, Pederzoli P: Prospective randomised pilot study of management of the pancreatic stump following distal resection. *HPB Surg* 1999;1:203–207.
- 24 Ohwada S, Ogawa T, Tanahashi Y, Nakamura S, Takeyoshi I, Ohya T, Ikeya T, Kawashima K, Kawashima Y, Morishita Y: Fibrin glue sandwich prevents pancreatic fistula following distal pancreatectomy. *World J Surg* 1998;22:494–498.
- 25 Wacławiczek H, Boeckl O: Pancreatic duct occlusion with fibrin sealant for the protection of the pancreatic digestive anastomosis following resection of the pancreatic head (experimental and clinical study); in Schlag G, Redl H: *General and Abdominal Surgery*. Berlin, Springer, 1994, vol 88, p 106.
- 26 Van Gulik T, Van Berge Henegouwen M, Gabeler E, Verbeek P, De Wit L, Obertop H, Gouma D: Leakage of the pancreatic anastomosis in 224 Whipple's resections. Incidence and prevention using systemic somatostatin or fibrin glue for temporary occlusion of the pancreatic duct. *European IHPBA Congress 'Athens 95'*. Bologna, Monduzzi, 1995, pp 539–542.
- 27 Marczell AP, Stierer M: Partial pancreaticoduodenectomy (Whipple procedure) for pancreatic malignancy: occlusion of a non-anastomosed pancreatic stump with fibrin sealant. *HPB Surg* 1992;5:251–259; discussion 259–260.
- 28 Lorenz D, Wolff H, Wacławiczek H: Pancreatic duct occlusion in resection treatment of chronic pancreatitis and cancer of the head of the pancreas. A 3-year follow-up study. *Chirurg* 1988;59:90–95.
- 29 Suc B, Msika S, Fingerhut A, Fourtanier G, Hay JM, Holmieres F, Sastre B, Fagniez PL: Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: prospective randomized trial. *Ann Surg* 2003;237:57–65.
- 30 Tran K, Van Eijck C, Di Carlo V, Hop WC, Zerbi A, Balzano G, Jeekel H: Occlusion of the pancreatic duct versus pancreaticojejunostomy: a prospective randomized trial. *Ann Surg* 2002;236:422–428; discussion 428.
- 31 Erdogan D, van Gulik TM: Evolution of fibrinogen-coated collagen patch for use as a topical hemostatic agent. *J Biomed Mater Res B Appl Biomater* 2008;85:272–278.
- 32 Albala DM: Fibrin sealants in clinical practice. *Cardiovasc Surg* 2003;11(suppl 1):5–11.
- 33 Knaebel HP, Diener MK, Wente MN, Buchler MW, Seiler CM: Systematic review and meta-analysis of technique for closure of the pancreatic remnant after distal pancreatectomy. *Br J Surg* 2005;92:539–546.
- 34 DeMets DL, Lan KK: Interim analysis: the alpha spending function approach. *Stat Med* 1994;13:1341–1352; discussion 1353–1346.
- 35 Champion HR, Fingerhut A, Escobar MA, Weiskopf RB: The role of data and safety monitoring in acute trauma resuscitation research. *J Am Coll Surg* 2007;204:73–83.
- 36 Gebhardt C, Stolte M, Schwill PO, Zirngibl H, Engelhardt W: Experimental studies on pancreatic duct occlusion with prolamine. *Horm Metab Res Suppl* 1983;9–11.
- 37 Di Carlo V, Chiesa R, Pontiroli AE, Carlucci M, Staudacher C, Zerbi A, Cristallo M, Braga M, Pozza G: Pancreatoduodenectomy with occlusion of the residual stump by neoprene injection. *World J Surg* 1989;13:105–110; discussion 110–111.
- 38 Konishi T, Hiraishi M, Kubota K, Bandai Y, Makuuchi M, Idezuki Y: Segmental occlusion of the pancreatic duct with prolamine to prevent fistula formation after distal pancreatectomy. *Ann Surg* 1995;221:165–170.
- 39 Little JM, Lauer C, Hogg J: Pancreatic duct obstruction with an acrylate glue: a new method for producing pancreatic exocrine atrophy. *Surgery* 1977;81:243–249.
- 40 Itoh T, Idezuki Y, Konishi T: Ethibloc-occlusion for prevention of pancreatic fistula after distal pancreatectomy. *J Jpn Soc Clin Surg* 1989;50:1526–1531.
- 41 Gall FP, Gebhardt C, Meister R, Zirngibl H, Schneider MU: Severe chronic cephalic pancreatitis: use of partial duodenopancreatectomy with occlusion of the pancreatic duct in 289 patients. *World J Surg* 1989;13:809–816; discussion 816–817.
- 42 Altman DG, Bland JM: Absence of evidence is not evidence of absence. *BMJ* 1995;311:485.