Role of Fibrin Sealants in Liver Surgery

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Key Words

Fibrin sealant • Hemostasis • Bile leakage • Liver resection

Abstract

Background: Fibrin sealants are widely used in liver surgery. The aim of this article is to review the literature on evidence of hemostatic and biliostatic capacities of different fibrin sealants in liver surgery. **Methods:** In PubMed, a literature search was done with the search terms 'fibrin sealant' or 'fibrin glue' combined with 'liver resection' or 'bile leakage'. Thirteen comparative fibrin sealant studies were selected. **Results:** In general, these studies have shown a reduced time to hemostasis when fibrin sealants were used. So far, only a few studies have been published that have focused on postoperative resection surface-related complications. There is no strong evidence that fibrin sealants reduce the incidence of bile leakage after liver resection. Important new evidence shows that bile contains profibrinolytic activity that causes lysis of the clot formed by the fibrin sealant at least in vitro. **Conclusions:** Fibrin sealants can be effective as an adjunct to achieve hemostasis during liver resections. However, considering lack of evidence on the efficacy of fibrin sealants in reducing postoperative resection surface-related complications, routine use of fibrin sealants in liver surgery cannot be recommended.

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Introduction

Advances in surgical techniques and patient care have led to improvement in outcome after liver resections [1, 2]. Despite these improvements, intraoperative bleeding from the resection plane of the liver and postoperative resection surface-related complications like bleeding, bile leakage and abscess formation remain a major problem [2–4]. Apparently, conventional surgical techniques cannot completely eradicate these complications. Therefore, covering the liver resection surface with a product that can seal both blood vessels and biliary radicals is an interesting concept. For this reason, fibrin sealants are widely used in liver surgery [5–7] despite scarce scientific evidence on the clinical effectiveness of these products [8, 9]. The aim of this article is to review the literature on evidence of hemostatic and biliostatic capacities of different fibrin sealants in liver surgery.

Methods

In PubMed, a literature search was done with the search terms 'fibrin sealant' or 'fibrin glue' combined with 'liver resection' or 'bile leakage'. Clinical studies were selected that compared fibrin sealants with control treatment. Controls were either no treatment or treatment with another type of topical hemostatic agent

or another type of fibrin sealant. Studies were selected that were published in English and focused on hemostatic or biliostatic end points. In total, 163 titles were left for abstract screening. Twelve clinical comparative studies were recognized; after checking cross-references, one more comparative study was recognized.

Different Types of Sealants

Fibrin sealants are a group of topical hemostatic products that mimic the final stages of the blood coagulation process (fig. 1). Fibrin sealants are two-component products, containing thrombin and fibrinogen. When mixed together during application of the sealants, thrombin cleaves the fibrinogen to monomers, which polymerize to form a fibrin gel [9, 10]. Fibrin sealants can come in two-component vials to form a glue (Tissucol®, Tisseel®, Quixil®, Evicel®, Crosseal®, Vivostat®, Beriplast®, Biocol®, Bolheal®, Hemaseel®), but they can also be carried on a matrix, the so-called carrier-bound fibrin sealants. Carrier-bound sealants are available in a solid form, consisting of a collagen fleece coated with a dry form of fibrinogen and thrombin (Tachosil®, Tachocomb®), and in liquid form containing thrombin and gelatin (Flo seal®) or thrombin and collagen (Costasis®).

While the basic components of most fibrin sealants are similar, different formulations and varying concentrations of the key components may cause differences between the products in fibrin clot formation. Apart from the concentration of thrombin and fibrinogen, the presence of antifibrinolytics, calcium concentration, the presence of other plasma proteins, ionic strength and temperature all affect the speed of clot formation and stability and adhesive strength of the clot that is formed [9, 11–13].

Clinical Studies on Fibrin Sealants in Liver Surgery

Kohno et al. [14] were the first to publish a randomized study on fibrin sealant in liver resection. The aim of the study was to compare clinical efficacy of two hemostatic agents on hemostasis and postoperative complications. They compared 31 patients receiving fibrin sealant glue (Beriplast) with 31 patients receiving a microcrystalline collagen powder (Avitene®) in elective liver resection. They showed equal hemostatic effects in both groups. A dry cut surface of the liver was obtained during surgery in 27 (87%) patients in the fibrin glue group and in 25 (81%) in the collagen group. Postoperative bleeding was

Fig. 1. General working mechanism of fibrin sealants (components fibrinogen and thrombin) mimicking blood coagulation process. TAFI = Thrombin-activatable fibrinolysis inhibitor; dashed lines = inhibiting effect; continuous lines = stimulating effect.

6% in both groups, and there were no differences in morbidity and mortality. Considering the fact that there were fewer patients with bile leakage from the resection surface of the liver in the fibrin sealant group (0 patients vs. 2 patients in the collagen group, n.s.), they concluded that fibrin sealants were more reliable than microcrystalline collagen powder in the postoperative course [14].

Noun et al. [15] randomized 82 patients comparing fibrin sealant glue (Biocol, 38 patients) on the liver resection plane with conventional hemostasis of the resection surface in 44 patients. The aim of the study was to evaluate the efficacy and safety of fibrin sealant after its application to the liver resection surface. A dry cut surface of the liver was obtained in 97% in the fibrin sealant group versus 81% in the conventional group ($p = 0.016$). There was no difference between the groups in the time to reach complete hemostasis. There was also no difference in the amount of perioperative blood transfusions. Postoperative morbidity and mortality in both groups were equal, although the mean total fluid drainage during the first 3 days and the bilirubin concentration in this fluid were significantly lower in the group with fibrin glue. They concluded that fibrin glue application to the hepatic stump after hepatic resection provides effective sealing [15].

A reduction in postoperative drain fluid production when fibrin sealants were applied on the resection plane

of the liver was confirmed in a pilot study by Eder et al. [16]. A fibrin sealant group (Tissucol or Tachocomb, 13 patients) was compared with a group of patients who did not receive fibrin sealant, only conventional hemostasis (12 patients). This was a small comparative non-randomized study, although both groups appeared to be comparable considering age, sex and extent of surgical resection. Drainage volumes were determined in 4-hour intervals through the first 24 h after surgery, showing favorable results in the fibrin sealant group [16].

Another randomized study showed a significant reduction in the amount of hemoglobin in postoperative drain production when fibrin sealant was used [17]. The use of fibrin sealant on the resection surface (Beriplast, 20 patients) was compared with conventional hemostasis of the resection surface in 20 patients in liver resection. The focus of the study was on the efficacy of fibrin sealant in reducing postoperative bleeding complications. The conclusion of this study was that fibrin sealant is useful in control of postoperative bleeding after liver resection [17].

More recently, Chapman et al. [18] compared the hemostatic performance of a composite of bovine microfibrillar collagen and bovine thrombin mixed with autologous plasma (Costasis, 38 patients) with the application of a collagen sponge (Instat®, 29 patients) on the hepatic resection margin, in a randomized fashion. There were no differences regarding transfusion requirements. The investigators did see a significant difference in the time to achieve hemostasis, favoring the fibrin sealant group. In all 38 patients in the fibrin sealant group, complete hemostasis was achieved within 10 min compared with only 69% of control subjects. The median time to controlled bleeding was significantly longer for control subjects [18].

A study with a similar primary end point was performed by Schwartz et al. [19] comparing the use of a fibrin sealant glue (Crosseal, 58 patients) with standard topical hemostatic agents (Actifoam®, Avitene, Gelfoam®, Oxygel®, Surgicel®, Surgicel Nu-Knit®, and Thrombinar®, total 63 patients). Application of fibrin sealant resulted in a statistically significant improvement in time to hemostasis compared to application of standard topical hemostatic agents. Secondary end point of this study was focused on postoperative resection surface-related complications. Postoperative complications (defined as reoperation for any reason, a diagnosis of abdominal fluid collections or bilious drainage for at least one day) were significantly lower in the fibrin sealant group (17.2%) compared to the control group (36%). The percentage of patients with abdominal collections was

significantly lower in the Crosseal group than in the control group (3.4 vs. 14.3%). In this publication, there were no further details of these results. The authors stated that there were no significant differences in intraoperative blood loss, duration of postoperative bilious drainage, percentage of patients with bile loss, volume of drainage fluid, and duration of drainage, though differences favored the fibrin sealant group [19].

Frilling et al. [20] reported on the hemostatic efficacy of a solid matrix fibrin sealant (Tachosil, 59 patients) versus argon beam coagulation of the resection surface (62 patients). This randomized multicenter study showed that fibrin sealant was superior to argon beam regarding time to hemostasis. Hemoglobin concentration at the 2nd day after surgery was significantly lower in the fibrin sealant group. Bile leakage was reported in 4 (7%) patients in the fibrin sealant group versus 2 (4%) patients in the argon beam group, which did not reach statistical significance. Overall, the frequency of adverse events did not differ between groups [20].

All the above studies mainly discussed the efficacy of fibrin sealants on hemostasis during hepatic resection. Figueras et al. [21] were the first to perform a study that primarily focused on postoperative complications. In a large single-center randomized trial, they compared fibrin sealant (Tisseel plus absorbable collagen sponge, 150 patients) with conventional hemostatic techniques in another 150 patients. Primary end points addressed bleeding complications and postoperative blood transfusion. Secondary endpoints were other resection surface-related complications and overall morbidity and mortality. There were no differences between groups in bleeding complications or postoperative transfusion rates (18 vs. 12%, fibrin sealant vs. control), overall drainage volumes, days of postoperative drainage, incidence of biliary fistula (10 vs. 11%) or postoperative morbidity (23 vs. 23%) [21].

Similarly, Berrevoet and de Hemptinne [7] did not observe any differences in postoperative resection surface-related complications in a retrospective comparative cohort study between two centers. They compared the use of no sealant in their own center (Ghent, Belgium, 222 patients) with the use of a solid matrix fibrin sealant (Tachocomb, Mulheim, Germany, 173 patients) in the other center in hepatic resections performed over a period of 6 years. Patient and surgical characteristics were comparable. There were no significant differences in postoperative blood transfusion, bile leakage and reoperation for bleeding [7]. Unfortunately, detailed information has not been published on this study.

Recently, a prospective controlled quasi-experimental study was published by Briceno et al. [22] that focused on postoperative complications after the use of fibrin sealant in liver resection. A solid matrix fibrin sealant (Tachosil, 57 patients) was compared with no sealant (58 patients). The use of fibrin sealant appeared to be effective in decreasing drainage volume, postoperative blood transfusion requirements, and moderate to severe postoperative complications. There was no difference between groups in the incidence of bile leakage. Unfortunately, patients were not randomized in this study. Instead, a 'closure' team decided whether to use fibrin sealant or to use conventional hemostatic techniques [22].

The most recent published randomized study on sealants in liver resection used a fibrin sealant glue (Tissucol, 29 patients) as a control versus the use of Plasmajet® (29 patients) on the raw surface of the liver after hepatic resection [23]. The study was designed as a pilot study. Plasmajet is a device that provides a high energy flow of ionized gas which seals small blood and lymph vessels. Instead of a positive impact of fibrin sealants, this report described a higher incidence of fluid collections requiring percutaneous drainage in the fibrin sealant group compared to the Plasmajet group. (20.6 vs. 3.4%, $p < 0.001$). Results of this study were not described in detail but pleural effusion was also counted as a fluid collection. Abdominal fluid collections were drained in 10.3 versus 3.4%; this difference was not significant [23].

Interestingly, two studies were published that compared two different types of fibrin sealants. Hayashibe et al. [24] published a retrospective historical cohort study comparing the use of fibrin sealant alone (fibrin glue, not further specified, 37 patients, cohort 2001–2003) with the use of the same fibrin sealant glue in combination with bio-absorbable polyglycolic acid (PGA) felt (51 patients, cohort 2003–2005). They observed more bile leakage in the group of fibrin sealant alone than in the fibrin sealant with PGA felt group (8.1 vs. 0%, $p = 0.03$). Their explanation for this phenomenon was that PGA felt is thought to stimulate attachment and sealing of bile ducts by fibrin glue and prevents early detachment of the fibrin glue from the cut surface of the liver [24]. Similar results were described in another retrospective historical cohort study, comparing two different fibrin sealants in split liver transplantation [25]. In the first cohort, fibrin glue was used (Tissucol, 16 patients, cohort 2003–2005); in the second, a solid matrix fibrin sealant was used (Tachosil, 16 patients, cohort 2005–2006). Bile leakage was seen in 43.7 versus 6.3% of patients, respectively ($p = 0.03$) [25]. Cohorts in this last study were not completely comparable

and sample sizes were low, but both studies suggest that there might be a difference between fibrin glues and solid matrix fibrin sealants.

Fibrin Sealants and Prevention of Bile Leakage

Overall, the incidence of bile leakage has not decreased over the years, and has been described in 1–14% of patients after liver resection [2, 4, 26, 27]. Risk factors for bile leakage are high-risk procedures with exposure of the major glissonian sheath [3, 4, 26, 28], resections combined with bilioenteric anastomosis [29, 30], size of resection plane [26], patient age [28], higher preoperative white blood cell count [28], and prolonged operation time [3, 28]. In a retrospective series of more than 600 patients, Capussotti et al. [4] showed an association between the application of fibrin sealant on the resection surface and a lower incidence of bile leakage ($RR = 0.38$, $p = 0.046$). As stated before, in clinical trials this effect has not been confirmed. Only limited research has been done to investigate the efficacy of fibrin sealants in reducing the incidence of bile leakage (table 1). So far, Figueras et al. [21] are the only group that performed a well-powered study on the use of fibrin sealants in liver resections, but this study did not show a difference in the incidence of bile leakage in sealant use versus no sealant. Studies that do show a reduction in bile leakage were either of poor methodological quality or were underpowered.

Even though in clinical studies fibrin sealants do not seem to reduce bile leakage, there are some studies that indicate that fibrin sealants may have the potential to seal bile ducts. Noun et al. [15] showed that the concentration of bilirubin in the drains was significantly lower in fibrin sealant versus no sealant, suggesting a sealing effect, but they did not report on the incidence of bile leakage (table 1). In experimental studies, fibrin sealants have mainly been tested as an adjunct to suture closure of the common bile duct. Results were contradictory; some studies showed a protective effect of fibrin sealants on bile leakage from the anastomosis of the common bile duct in a dog model [31, 32], whereas another study in a pig model did not [33]. Instead of using a fibrin sealant, Wise et al. [34] tested a synthetic sealant (polyethylene glycol/collagen biopolymer) in an experimental liver resection model in pigs. In all pigs, they transected the common bile duct and performed an incomplete end-to-end choledochocholedochostomy over a T-tube, leaving an anterior defect of one sixth of the circumference. In 9 pigs, sealant was applied around the circumference of the anastomo-

Table 1. Clinical comparative studies on fibrin sealant in liver resection structured by different types of fibrin sealant

First author	Inclusion	Comparison	Design	Time to hemostasis min	Complete hemostasis %	Total drainage days	Volume drain ml	Hb g/100 ml	Bilirubin	Morbidity %	Mortality %	Postoperative		Reoperation, %	Bile leakage %
												blood transfusion, %	abdominal fluid collections, %	bleeding %	
Liu [17]	20 FSG vs. 620 NS		RCT	-	-	-	-	8.1 15.6 (g/day)	-	-	-	-	-	-	-
Noun [15]	38 FSG vs. 44 NS		RCT	26 ^a 26	97 81 ^b	-	242 505 ^b (3 days)	0.8 1.1	24 65 ^b	-	-	18 25 (periop.)	16 20	-	-
Eder [16]	13 FSG vs. 12 NS		comp. cohort	-	-	-	350 ^c 950 ^b (day 1)	-	-	-	-	-	-	-	-
Kohno [14]	31 FSG vs. 31 collagen		RCT	-	87 81	7.2 6.3	164 156 (day 1)	-	-	39 45	10 13	-	0 3 (abscess)	- 6 6	3 3
Schwartz [19]	58 FSG vs. 63 other ^d		RCT	4.7 7.8 ^b	91 70 ^b	no diff.	no diff.	-	-	17 ^e 36 ^b	2 10	-	3 14 ^b	-	no diff.
Gugenheim [23]	29 FSG vs. 29 PJ		RCT	-	-	-	-	-	-	-	10 7	3 3	10 3 (drained collection)	- 0 0	3 0
Figueras [21]	150 FSG + collagen vs. 150 NS		RCT	-	-	7.9 7.1	1,180 960 (overall)	-	-	23 23	4 1	18 12	8 4 (abscess)	1 1	6 3 10 11
Chapman [18]	38 FSL vs. 29 collagen		RCT	2.5 6.0 ^b	100 69 ^b	-	-	-	-	-	0 7	no diff.	-	no diff.	-
Briceno [22]	57 FSS vs. 58 NS	prosp. quasi exp.		-	-	3.8 6.1 ^b	691 1,125 ^b (overall)	-	-	18 43	0 0	19 7	7 4 (drained collection)	5 0	10 7
Berrevoet [7]	173 FSS vs. 222 NS	comp. cohort		-	-	-	-	-	-	-	-	no diff.	-	3 0	no diff. 2 3
Frilling [20]	59 FSS vs. 62 argon	RCT		3.9 6.3 ^b	97 90	6.0 5.7	525 496 (day 1)	3.3 3.6	-	24 11	10 3	-	7 5	-	7 3
Hayashibe [24]	37 FSG vs. 51 FSG + PGA	comp. cohort		-	-	-	-	-	-	-	-	-	-	3 0	8 0 ^b
Toti (Split LT) [25]	16 FSS vs. 16 FSG	comp. cohort		-	-	-	-	-	-	-	-	-	-	-	6 43 ^b

FSG = Fibrin sealant glue (Tissucol, Tisseel, Quixil, Crosseal, Biocol® or Beriplast); FSL = fibrin sealant + liquid matrix (Costasis); FSS = fibrin sealant + solid matrix (Tachosil, Tachocomb); NS = no sealant; RCT = randomized controlled trial; Comp. cohort = comparative cohort study; split LT = split liver transplantation; no diff. = no difference, as stated in publication, no numbers known; PJ = Plasmajet.

^a Time to complete hemostasis and biliostasis. ^b Statistically significant. ^c From numbers documented in figure publication. ^d Other refers to other topical hemostatic agents. ^e Combined morbidity endpoint: % reoperation for any reason, a diagnosis of abdominal fluid collections or bilious drainage for at least 1 day.

sis. Nothing was applied in the control group. Bile leakage was seen in 5 out of 9 (56%) in the control group versus 1 out of 9 (11%) in the sealant group ($p < 0.05$) [34]. In conclusion, use of this synthetic sealant resulted in a reduction in the incidence of bile leakage, which could not clearly be shown in other studies when fibrin sealants were used. Lack of evidence in the experimental fibrin sealant studies might also be attributable to a poor design of these studies.

Erdogan and van Gulik [35] suggested adhesive strength of the fibrin sealant to be an important factor in the prevention of bile leakage. They performed an experimental study in a partial liver resection model in pigs. They compared the use of a solid matrix fibrin sealant (Tachosil, 4 pigs) with the use of a fibrin sealant glue (Tissucol, 4 pigs) on the liver resection surface [35]. A catheter was introduced in the common bile duct. Two hours after application of the sealant, pressure in the common bile duct was increased with the use of saline. The pressure that could be resisted with the liquid fibrin sealant was significantly lower compared to solid matrix fibrin sealant. This study showed that the adhesive strength of this solid matrix sealant was better than the fibrin glue [35, 36]. Whether the adhesive strength of these solid matrix sealants is intrinsic to the product or caused by the fact that the sealant is applied to the surface by pressure has not been investigated. It has been postulated that the adhesive strength of products that can be applied with pressure are theoretically better than products that are applied without pressure, like the liquid fibrin sealants [9]. This could also be concluded from the two clinical studies by Hayashibe et al. [24] and Toti et al. [25]. Both studies compared different sealants or different combination and application of products. Again, from these studies it is not clear whether the possible differences in effect on bile leakage between fibrin sealant glues and solid matrix fibrin sealants are caused by the products themselves or by the differences in application (pressure vs. no pressure).

The stability of fibrin sealants on dissected bile ducts has not been studied in detail. The study previously discussed by Erdogan and van Gulik [35] used saline to increase pressure in the common bile duct instead of bile. Interestingly, there are indications from the literature that bile interferes with the hemostatic process, a process which is mimicked by the fibrin sealant when applied to the resection surface of the liver. In 1919, Haessler and Stebbins were the first to report on the anticoagulant effect of bile [37]. More than 50 years later, bile was found to contain fibrinolytic activity, and a protein referred to

as bilokinin was isolated [38–41]. Several studies identified the presence of different fibrinolytic proteins including plasminogen, plasminogen activator inhibitor type 1 (PAI-1) and plasminogen activator (tPA) in human bile [42–44]. Although these studies did not address whether these proteins were functional, they do raise the question whether bile has a lytic effect on fibrin sealants or not.

Recently, our group investigated the effect of human bile on the stability of different fibrin sealants and plasma clots *in vitro* [45]. Addition of bile to fibrin sealants accelerated lysis of *in vitro* clotted fibrin sealants. The lysis-promoting activity of bile could be partially blocked by immunodepletion of tissue-type plasminogen activator (tPA). Lytic activity was completely blocked when both tPA and lysine-binding proteins were immunodepleted, which suggests that tPA and plasminogen are responsible for the lysis-promoting effect of human bile. The lytic effect of bile could not be blocked by the addition of high-dose PAI-1, and we showed that tPA in a biliary environment is unsusceptible to PAI-1 inhibition. Results of this experimental study suggest that the presence of tPA and other fibrinolytic proteins in human bile cause lysis of plasma and fibrin glues [45]. Whether these effects account for all fibrin sealants or only for the fibrin sealants tested in this study, remains to be seen.

These lytic effects of bile on fibrin sealants have not been proven *in vivo*, but might be an explanation why there is no evidence so far for the efficacy of fibrin sealants in reducing bile leakage after liver resection. Future studies are needed that focus on the effect of fibrin sealants on the incidence of bile leakage. We are currently awaiting the results of a Dutch multicenter randomized study on the effect of fibrin sealants in reducing resection surface-related complications (FRESCO study; controlledtrials.com: ISRCTN85205641). Future focus of bile leakage reduction may lie in the development of synthetic sealants.

In conclusion, fibrin sealants are widely used in liver surgery. Several fibrin sealant studies were performed in the field of liver surgery to analyze their efficacy on hemostasis, postoperative drain fluid production and resection surface-related complications like bile leakage, bleeding and abscess formation. In general, these studies have shown a reduced time to hemostasis when fibrin sealants were used. However, few studies have been published so far that focused on postoperative resection surface-related complications, like bile leakage, bleeding or abscess formation. Although different types of fibrin sealants showed different results, there is no strong evidence that fibrin sealants reduce the incidence of bile

leakage after liver resections. Studies that did show a reduction in resection surface related complications were either of poor methodological quality or were underpowered. Important new evidence shows that bile contains profibrinolytic activity that causes lysis of the clot formed by the fibrin sealant at least in vitro. Future studies are needed to further analyze the lysis of different fibrin sealants (fibrin glues vs. solid matrix fibrin sealants) in vitro

and in vivo by human bile. Apart from improvement of surgical techniques, a possible solution to the problem of bile leakage after liver resection may lie in the development of safe and ready to use synthetic sealants instead of fibrin sealants. Since there is no evidence on the efficacy of fibrin sealants in reducing postoperative resection surface-related complications, routine use of fibrin sealants in liver surgery cannot be recommended.

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