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REVIEW ARTICLE

Fibrin sealants and topical agents in hepatobiliary and pancreatic surgery: a critical appraisal

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Abstract
Introduction Fibrin sealants and topical hemostatic agents have been used extensively in hepatobiliary and pancreatic (HPB) surgery to promote coagulation and clot formation decreasing the need for allogeneic blood transfusion and to act as tissue sealants, ideally preventing biliary, enteric, and pancreatic leaks.
Results Current literature has demonstrated some favorable outcomes using many different products for application in the field of HPB surgery. However, critical findings exist demonstrating lack of reproducible efficacy or benefit. In all, many clinical trials have demonstrated effectiveness of fibrin sealants and other agents at reducing the need for intraoperative and postoperative blood transfusion. Ability to effectively seal tissues providing biliostatic effect or preventing postoperative fistula formation remains debated as definitive evidence is lacking.
Conclusions In the following invited review, we discuss current literature describing the use of topical agents and fibrin sealants in liver and pancreas surgery. We summarize major contemporary clinical trials and their findings regarding the use of these agents in HPB surgery and provide evidence from the preclinical literature as to the translation of these products into the clinical arena.

Keywords Fibrin · Sealant · Hepatobiliary · Hemostasis · Pancreas · Liver

Introduction

Morbidity and mortality in hepatobiliary and pancreas (HPB) surgery have increasingly improved over the past two decades, particularly in high volume centers [1]. Better operative techniques, including the widespread application of minimally invasive HPB surgery, enhanced critical care in the postoperative period, and new technologically advanced materials designed to aid and improve hemostasis both in and out of the operating room continue to change this field. Specific challenges associated with HPB surgery include both intraoperative and postoperative include bleeding from raw liver and pancreas resection surfaces, bile leak, and pancreatic duct leak leading to pancreatic fistula [2]. An increasing application of topical agents and fibrin sealants for use in HPB surgery have been previously described and requires critical appraisal of the literature pertaining to these agents and their efficacy in this unique operative setting [3, 4, 2].

In the following invited review article, we discuss the use of topical hemostatic agents and fibrin sealants in hepatobiliary and pancreas surgery. We describe agents currently available on the market and the current body of literature describing the use of these products in the HPB surgery field. We include evidence from the preclinical literature regarding the efficacy of these products and their translation to the clinical application.

Types of fibrin sealants and topical agents

Fibrin sealants and topical hemostatic agents have been shown to be effective for many different applications. While primarily helping to control perioperative blood loss, they may also control blood loss in areas that are difficult to suture or provide support for sutures in friable, bleeding tissues [5, 6]. Additional evidence supports the use of these agents for sealing cut surfaces preventing tissue leaks and as an adjunct to promote wound healing [7, 8]. In a Cochrane-based meta-analysis of the use of fibrin sealants across many different surgical subspecialties, 18 different trials have found a

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significant reduction in allogenic blood transfusion with the use of fibrin sealants [9].

Available types of fibrin sealants and topical hemostatic agents have evolved through the years to complex drug delivery systems and varying application systems (Table 1). Most commercially available fibrin sealants contain two components: human fibrinogen and human- or bovine-derived thrombin. The mixture of the two components forms a cross-linked insoluble fibrin clot at the site of application [10]. Some products include the addition of an antifibrinolytic agent such as aprotinin or tranexamic acid to prevent enzymatic degradation of the clot formed or special filtration techniques to reduce plasminogen concentration [10]. Newer formulations include carrier-bound fibrin sealants, which have provided new application methods for effective hemostasis. These methods provide drug delivery systems often in the form of a patch or solid application material to cover large surface areas. TachoSil is one such product and consists of an equine collagen fleece patch carrying human fibrinogen and thrombin [11].

Other topical hemostatic agents contain different biological and synthetic materials used alone or in combination to promote intraoperative hemostasis (Table 2). Oxidized cellulose-based products (Surgicel, Fibrillar etc.) have been on the market in the USA for over 40 years and are commonly used for intraoperative hemostatic control. This was followed by a series of bovine collage and porcine-derived gelatin-based products introduced in the 1980s and 1990s. Newer formulations of hemostatic agents are derived from polyethylene glycol, cyanoacrylate, or polysaccharides. Thrombin is also available in human-derived, bovine, and recombinant forms for direct application in the setting of diffuse oozing or bleeding [12]. When combined with bovine- or porcine-derived gelatin (FloSeal, Surgiflo, Costasis), the flowable matrix-based application can be used in both laparoscopic and open surgery to provide hemostatic control. We have found that many of these topical hemostatic agents provide better intraoperative blood loss control for active bleeding as compared to topical fibrin sealants that may be better in situations in which minimal oozing is observed.

Table 1 Commercially available fibrin-based sealants [2]

Product	Manufacturer	Description	Indication
EVARREST	Ethicon, Inc, a Johnson & Johnson Company, Somerville, NJ	Human fibrinogen and human thrombin sealant patch	For use with manual compression as an adjunct to hemostasis for soft tissue bleeding during open retroperitoneal, intra-abdominal, pelvic, and non-cardiac surgery.
Quixil/Crosseal	OMRIX Biopharmaceutical Ltd., Kiryat-Ono, Israel	Two vials containing human thrombin and human fibrinogen	For use in obtaining liver hemostasis and in orthopedic surgery
TachoSil	Nycomed GmbH, Linz, Austria	A ready-to-use surgical patch composed of a dry collagen sponge made from horse tendons, and on one side coated with human fibrinogen and thrombin	An adjunct to hemostasis in cardiovascular surgery when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.
Evicel	Johnson & Johnson, Somerville, NJ; OMRIX biopharmaceuticals Ltd. Kiryat Ono, Israel	Fibrin sealant—human pooled	An adjunct to hemostasis for use in patients undergoing surgery (liver and vascular surgery are also separately indicated) when control of bleeding by conventional surgical techniques is ineffective or impractical.
CryoSeal Fibrin Sealant System	Thermogenesis, Rancho Cordova, CA	Fibrin sealant—human	An adjunct to hemostasis on the incised liver surface in patients undergoing liver resection when control of bleeding by standard surgical techniques is ineffective or impractical.
Vitagel	Orthovita, Malvern, PA	Fibrin sealant- individual units of plasma, bovine collagen, and bovine thrombin	For use during surgical procedures (except neurosurgery and ophthalmic surgery) as an adjunct to hemostasis when control of bleeding by ligature or other conventional procedures is impractical or ineffective.
TISSEEL	Baxter Healthcare Corporation, Westlake Village, CA	Fibrin sealant- human pooled	An adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries. TISSEEL is satisfactory for use in fully heparinized patients undergoing cardiopulmonary bypass. Also indicated as an adjunct to prevent leakage from colonic anastomosis following the reversal of temporary colostomies.

Table 2 Commercially available topical hemostatic agents [2]

Product	Manufacturer	Description	Indication
Thrombin-containing products			
Thrombin-JMI	King Pharmaceuticals, Bristol, TN	Bovine thrombin	Aid in hemostasis whenever oozing blood or minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical.
Evithrom	Johnson & Johnson, Somerville, NJ	Lyophilized human pooled thrombin	Aid in hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical.
Recothrom	Zymogenetics, Seattle, WA	Recombinant thrombin	Aid in hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical.
FloSeal™ Hemostatic Matrix	Baxter Healthcare Corporation, Hayward, CA	Flowable bovine gelatin matrix and licensed human thrombin	In surgical procedures (other than ophthalmic) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.
CoStasis	Cohesion Technologies Inc., Palo Alto, CA	Flowable bovine collagen and licensed bovine thrombin	In surgical procedures (other than neurological, ophthalmological, and urological) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.
Surgiflo	Johnson & Johnson, Somerville, NJ	Porcine gelatin with or without thrombin	In surgical procedures (except ophthalmological) for hemostasis, when control of capillary, venous and arteriolar bleeding by pressure, ligature, and other conventional procedures is ineffective or impractical.
Non-thrombin-containing products—collagen, cellulose, gelatin, etc.			
Progel	Davol, Warwick, RI	Human serum albumin and polyethylene glycol	For use in air sealing leaks during pulmonary surgery.
Veriset	Covidien Inc., Mansfield, MA	Oxidized cellulose backing with buffer salts, trilysine, and polyethylene glycol	For use in general and plastic surgery for hemostasis.
Arista AH	Medafor, Minneapolis, MN	Polysaccharide spheres	For use in surgical procedures (except neurological and ophthalmological) as an adjunctive hemostatic device to assist when control of capillary, venous, and arteriolar bleeding by pressure, ligature, and other conventional procedures is ineffective or impractical.
Avitene Ultrafoam sponge and flour	Bard, Murray Hill, NJ	Collagen based absorbable hemostatic	For all surgical procedures including neurosurgery and urology as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.
Hemostase MPH	Cryolife, Kennesaw, GA	Absorbable powder hemostatic	In surgical procedures (except neurological and ophthalmological) as an adjunct hemostatic device when control of capillary, venous, and arteriolar bleeding by conventional means proves ineffective or impractical.
Duraseal	Covidien, Waltham, MA	Single polyethylene glycol	An adjunct to sutured dural repair during cranial surgery to provide watertight closure. In 2011 additional approval for spine.
CoSeal	Baxter Healthcare Corporation, Hayward, CA	Two polyethylene glycols	For use in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage.

Table 2 (continued)

Product	Manufacturer	Description	Indication
BioGlue	Cryolife, Kennesaw, GA	Bovine albumin & 10 % glutaraldehyde	Adjunct to standard methods of achieving hemostasis (such as sutures or staples) in adult patients in open surgical repair of large blood vessels such as aorta or the femoral and carotid arteries.
OMNEX	Ethicon, Inc, a Johnson & Johnson Company, Somerville, NJ	Two cyanoacrylate monomers	For use in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage.
Surgifoam sponge and powder	Johnson & Johnson, Somerville, NJ	Porcine gelatin sponge	In surgical procedures (other than neurological, urological, and ophthalmological surgery) as an adjunct to hemostasis when control of capillary, venous and arteriolar bleeding by pressure, ligature, and other conventional procedures is ineffective or impractical.
Hemopad Novacol	Datascope Corp., Montvale, NJ	Bovine collagen	As a hemostatic device, when control of capillary, venous, and arteriolar bleeding by pressure, ligature, and other conventional procedures is either ineffective or impractical.
Helistat, Helitene	Integra Life Science, Plainsboro, NJ	Bovine collagen	In surgical procedures (other than ophthalmological and urological surgery) as an adjunct to hemostasis when control of bleeding by standard surgical procedure is impractical.
Instat, Instat MCH	Johnson & Johnson, Somerville, NJ	Purified and lyophilized bovine dermal collagen	In surgical procedures (other than urological and ophthalmological surgery) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.
Gelfoam sponge and powder	Pharmacia, Kalamazoo, MI	Porcine gelatin molded into a sponge	An aid in hemostasis, when control of capillary, venous, and arteriolar bleeding by pressure, ligature, and other conventional procedures is either ineffective or impractical.
CollaStat	Integra Life Sciences Corporation, Plainsboro, NJ	Absorbable bovine collagen sponge	In surgical procedures (other than ophthalmological and urological surgery) as an adjunct to hemostasis when control of bleeding by standard surgical procedure is impractical.
Surgicel, SURGICEL Fibrillar, and Nu-Knit	Johnson & Johnson, Somerville, NJ	Sponge of oxidized cellulose	Adjunct in surgical procedures to assist in control of capillary, venous, and small arterial hemorrhage when standard surgical techniques are ineffective or impractical.

Properties of fibrin sealant agents may allow for enhanced tissue adhesion and lead to better tissue sealing and potentially decreased postoperative leakage of bile or pancreatic fluid. Properties of many other hemostatic agents serve for just that purpose, providing hemostasis quickly and effectively with decreased ability for tissue sealant or adhesive effect. Choice of topical agent to be used intra-operatively should be based upon the desired effect and the unique operative situation.

Liver preclinical

To evaluate effectiveness of hemostatic agents in animal models of liver surgery, several trials have demonstrated effectiveness of topical-based fibrinogen thrombin and collagen applications in promoting hemostasis [13]. Animal models have demonstrated the effectiveness of a fibrinogen/thrombin patch in achieving hemostasis in the setting of blunt liver injury and severe coagulopathy [14]. Preclinical models have also been used to study effectiveness of bile duct sealing using liquid fibrin sealant or fibrin collagen patch with increased pressure in the common bile duct [15]. In this series, fibrin collagen patch resisted significantly higher intraductal pressures prior to evidence of bile leakage as compared to liquid fibrin sealant [15].

Liver clinical

Current attitudes regarding the use of fibrin sealants for hemostasis in liver surgery have demonstrated an increasing trend towards the use of these products by HPB surgeons for

hemorrhage control. In a study published in 2013, UK hepatobiliary specialists were surveyed and asked to comment on their use of hemostatic agents during liver resection; of the respondents, 62 % routinely used these products and 33 % used them occasionally [16]. Those surveyed also felt manufactured hemostatic agents played a major role in achieving hemostasis (64 %), with preference given to fibrin-based products by 27 % of survey respondents [16]. Likely, most surgeons find these products safe and at least somewhat effective, and as long as they are not cost prohibitive and readily available, they will continue to use them in practice. These findings are echoed from a previous study in which Dutch surgeons were surveyed regarding the use of topical hemostatic agents in liver surgery [4]. Similar findings were reported in that 87 % used hemostatic agents after resection of liver parenchyma, 57 % used them routinely, and as many as 45 % of the surveyed Dutch surgeons believed fibrin sealants reduce liver surface-related complications [4].

In a meta-analysis review of the benefits of fibrin sealant after liver resection, Ding and colleagues conclude mixed results, namely, evidence exists from randomized trials that fibrin sealant is superior to other topical hemostatic agents and argon beam coagulation in controlling intraoperative hemorrhage [17]. Ultimately, there was no significant benefit to fibrin sealant use in "reducing amount of drainage, drainage duration, transfusion requirements, bile leakage, rebleeding and mortality" [17]. A similar review of fibrin sealants in liver surgery published in 2012 concludes many of the same findings [18]. Time to achieve hemostasis in liver surgery is reduced when fibrin sealants are applied, but no strong evidence exists that fibrin sealants reduce incidence of bile leakage after liver resection, and this may be due to a lytic effect of bile on the fibrin-induced clot [18]. An additional meta-analysis describes the hemostatic and biliostatic efficacy of fibrin sealants in elective liver surgery and finds that while time to hemostasis may be reduced intra-operatively, this does not translate to improved perioperative outcomes or reduced incidence of postoperative hemorrhage or bile leak with routine use of fibrin sealants [19].

Of the carrier-bound fibrin sealants, collagen sponge delivery systems have been studied extensively for application in liver-related surgery, likely because the large surface area allows for easy, even coverage on raw cut surfaces. In a randomized prospective trial comparing TachoSil® to argon beam coagulation for hemostasis during liver resection, TachoSil® was found to significantly reduce time to hemostasis [11]. As compared to oxidized cellulose matrix Surgicel®, TachoSil® was not associated with reduced overall complication rate in liver surgery, but when patients were stratified into those undergoing major hepatic resection as compared to minor hepatic resection, a reduction was seen in overall complications and liver surgery specific complications as compared to Surgicel®[20]. TachoSil has also been found to be associated with reduction of postoperative bile leak following elective liver resection and liver trauma [21].

Some of the current literature would argue against the use of fibrin sealants in liver surgery as providing no significant efficacious benefit. The largest series comparing the use of fibrin sealant (Tissucol®) and a collagen sponge applied to the raw liver surface edge as compared to no application was reported [22]. This series found no differences in postoperative outcomes specifically including transfusion rates, drainage volumes, or evidence of biliary fistula [22]. In 2012, a randomized controlled trial was performed in 310 non-cirrhotic patients who underwent liver resection; prophylactic fibrin sealant (Crosseal®) was applied to the cut liver surface in half and no sealant in the other group [23]. There was no difference in resection surface-related complications, bile leakage, or CT scan demonstrated fluid collections between the two groups in this study [23]. However, in findings published in 2004 in which Crosseal® was administered by spray application to liver cut surface following resection, there was a significantly reduced time to achieve hemostasis [24]. So perhaps the argument can be made in favor of fibrin sealants and their ability to achieve immediate intraoperative hemostasis with some reservation on postoperative primary complications from liver-related surgery.

Specifically focusing on incidence and prevention of bile leakage after liver resection, Kobayahsi and colleagues reported a low incidence of bile leak after liver resection from cut surface (raw liver edges) when applying a polyglycolic acid felt to cover raw liver defects [25]. This was compared to raw liver surface edges covered with a conventional fibrin-coated collagen fleece [25]. In the Italian literature, retrospective analysis of 610 liver resections reported that application of fibrin glue significantly reduced postoperative bile leakage and more so found it was an independently associated protective factor for the prevention of postoperative bile leak [26]. A review article describing the use of hemostatic agents specifically for prevention of biliary leakage was published by Erdogan and colleagues [27]. They include description of a French multicenter randomized series, in which they found lower postoperative drain fluid amounts and lower concentration of bilirubin present in the fluid when fibrin glue was applied to cut surface edges, but did not show overall lower leakage rates or intra-abdominal fluid collections with fibrin sealant application [28]. Similar to the Kobayashi trial, Hayashibe and colleagues were able to significantly drop rates of bile leakage from cut resection surfaces when fibrin glue was combined with a bioabsorbable polyglycolic acid sheet to the cut resection surface [29].

The increasing use of laparoscopic techniques for HPB surgery has also encouraged the use of laparoscopic application of fibrin sealants and hemostatic agents. This may be due to the fact that technical success in laparoscopic liver surgery requires careful intraoperative control of bleeding to avoid

Table 3 Summary of major and comparative clinical trials using fibrin sealants and topical agents in HPB surgery

Authors, reference	Study design	Product used	Procedure, study groups	Findings
Liver				
Briceno et al. [7]	Prospective randomized	Carrier-bound fibrin sealant (TachoSil)	Major hepatectomy TS n=25 Control n=28 Minor hepatectomy TS n=32 Control n=30	Decreased rates of drain output, postoperative blood transfusion, and moderate to severe complications with the use of fibrin sealant.
Figueras et al. [22]	Prospective randomized	Fibrin glue	Hepatic resection FG n=150 Control n=150	No difference in overall drainage volumes, similar incidence of postoperative morbidity, similar incidence of biliary fistula.
Schwartz et al.[24]	Prospective randomized	Fibrin sealant (Crosseal) vs. standard topical hemostatic agents	Hepatic resection FS n=58 Control n=63	Reduced time to achieve hemostasis following liver resection with use of fibrin sealant.
De Boer et al. [23]	Prospective randomized	Fibrin sealant (Quixil)	Hepatic resection FS n=156 Control n=154	No reduction in incidence or severity of postoperative bile leak or other surface-related complications with application of fibrin sealant.
Ollinger et al. [50]	Prospective randomized	Hemostatic patch (Veriset) vs Fibrin sealant patch (TachoSil)	Hepatic resection HP n=32 Control n=18	Faster rate of hemostasis with use of hemostatic patch during open liver resection.
Zacharias and Ferreira [20]	Retrospective cohort	Fibrin sealant patch (TachoSil) vs Oxidized cellulose (Surgicel)	Hepatic resection FS n=64 Control n=69	No reduction in overall complication rate following all liver resections with use of fibrin sealant patch except in major hepatectomy.
Kobayashi et al. [31]	Retrospective cohort	Fibrin sealant with polyglycolic acid felt	Laparoscopic hepatectomy FS + PGA felt n=18 Control n=22	No significant differences between groups.
Kobayashi et al. [25]	Retrospective cohort	Fibrin sealant with polyglycolic acid felt vs Fibrin coated collagen fleece	Hepatic resection FS + PGA felt n=34 FCCF n=39	Reduced rate of bile leak in the group in which FS + PGA felt was applied following liver resection.
Frilling et al. [23]	Prospective randomized	Carrier bound fibrin sealant (TachoSil) vs Argon beamer	Hepatic resection TS n=59 AB n=62	TachoSil was superior to argon beam coagulation in obtaining fast and effective hemostasis.
Liu et al. [51]	Prospective randomized	Fibrin sealant glue	Hepatic resection FS n=20 Control n=20	Reduced postoperative bleeding in the group in which fibrin glue was applied.
Hayashibe et al. [29]	Retrospective cohort	Fibrin glue with bioabsorbable polyglycolic acid sheet vs Fibrin glue	Hepatic resection FG + PGA sheet n=51 FG n=37	Decreased rate of bile leak after application of fibrin glue and polyglycolic acid sheet.
Toti et al. [52]	Retrospective cohort	Carrier bound fibrin sealant (TachoSil) vs Fibrin glue	Split liver transplantation TS n=16 FG n=16	Reduction in split liver surface bile leaks with the use of TachoSil.

Table 3 (continued)

Authors, reference	Study design	Product used	Procedure, study groups	Findings
Chapman et al.[53]	Prospective randomized	Fibrin sealant plus liquid matrix (Costasis) vs Collagen sponge	Hepatic resection FSL n=38 Control n=29	Significantly faster control of hemostasis with use of fibrin sealant liquid.
Pancreas				
Satoi et al. [54]	Prospective non-randomized	Polyglycolic Acid Mesh and Fibrin glue	Pancreaticoduodenectomy PGA + FG n=50 Control n=78	No significant benefit in reduction of POPF
Mita et al. [49]	Retrospective, non-comparison	Fibrin adhesive (TachoComb)	Distal pancreatectomy TC n=25 Control n=0	20 % incidence of pancreatic fistula, no comparison performed
Mita et al. [55]	Retrospective, non-comparison	Fibrin adhesive (TachoComb)	Pancreaticoduodenectomy TC n=40 Control n=0	20 % incidence of pancreatic fistula, no comparison performed
Lillemoe et al. [42]	Prospective randomized	Fibrin glue	Pancreaticoduodenectomy FG n=59 Control n=66	Lower rate of POPF in FG arm (26 vs 30 % but not significant)
Montorsi et al. [44]	Prospective randomized	TachoSil	Distal pancreatectomy TS n=145 Control n=130	TachoSil had no effect on rate of POPF
Martin and Au [46]	Prospective randomized	Fibrin glue (TISSEEL)	Pancreaticoduodenectomy T n=32 Control n=25	Fibrin glue did not reduce incidence of anastomotic leak
Conaglen and Collier [48]	Retrospective cohort	Fibrin glue	Pancreaticoduodenectomy FG n=32 Control n=157	No pancreatic leaks or mortalities in FG arm since technique adopted
Ochiai et al.[47]	Retrospective Cohort	Polyethylene glycolic acid felt and fibrin glue	Pancreaticoduodenectomy PGA felt n=18 Control n=36 Distal pancreatectomy PGA felt n=26 Control n=37	Statistically significant reduction of POPF following introduction of PGA felt and fibrin glue to augment both procedures
Carter et al.[45]	Prospective randomized	Falciform ligament patch and fibrin glue	Distal pancreatectomy FL + FG n=54 Control n=55	No reduction in POPF with addition of falciform ligament patch and fibrin glue
Marczell et al.[56]	Retrospective	Fibrin glue (TISSEEL)	Pancreaticoduodenectomy FG n=44 Control n=22	Significantly higher rates of perioperative morbidity and mortality in control groups
Kram et al.[57]	Retrospective	Fibrin glue	Pancreatic trauma FG n=10 Pancreaticointestinal anastomosis FG n=5	No pancreatic fistulas after any operation following application of fibrin glue. No control comparison
Fisher et al.[43]	Retrospective cohort	BioGlue	Pancreaticoduodenectomy BG n=23 Control n=21	Higher rates of postoperative pancreatic fistula in the patients who received BioGlue sealant, i.e., no reduction of POPF.

Table 3 (continued)

Authors, reference	Study design	Product used	Procedure, study groups	Findings
			Distal pancreatectomy BG $n=9$ Control $n=11$	
Suc et al.[38]	Prospective randomized	Fibrin glue	Pancreaticoduodenectomy Distal pancreatectomy FG $n=102$ Control $n=80$	Ductal occlusion with fibrin glue does not reduce rate or severity of intra-abdominal complications after pancreatic resection.
Suzuki et al.[36]	Prospective randomized	Fibrin glue	Distal pancreatectomy FG $n=26$ Control $n=30$	Reduced rate of pancreatic fistula in fibrin glue application group ($p=0.04$).
Both				
Nanashima et al.[58]	Prospective	Fibrin glue	Hepaticojejunostomy FG $n=228$ NFG $n=94$ Pancreaticojejunostomy FG $n=113$ NFG $n=24$	Use of fibrin glue did not prevent biliary or pancreas fistulas.

obscuring visualization. Even small amounts of unmanaged bleeding may provide a cause for conversion to open surgery, so topical hemostatic agents may provide a direct role in successful laparoscopic liver surgery [30]. As a result of this trend towards minimally invasive surgery, many companies have adapted applicator devices or changed product design to ease application of hemostatic agents via minimally invasive techniques. Of the published literature, a non-inferiority study regarding the use of polyglycolic acid felt in laparoscopic liver surgery was not associated with any significant differences as compared to the group identified before fibrin sealant use [31]. Despite this, we believe the predominant trend towards minimally invasive surgery will likely continue to afford adaptations in products designed to control hemostasis via minimally invasive application.

Pancreas clinical

Fibrin sealants and topical agents have gained an increasing use following pancreatectomy procedures for intraoperative hemostasis control but more so, for the prevention of postoperative pancreatic fistula (POPF). Rates of pancreatic fistula formation remain highly variable based upon the procedure type, method of pancreatic transection, and institutional clinical volume. By and large, accepted postoperative pancreatic fistula rates range between 5 and 30 % [32], and vary in severity from chemically detected but requiring no intervention, to pancreatic leaks with severe clinical sequelae requiring intervention as defined by the ISGPF guidelines [33]. Efforts to improve pancreatic fistula rates have focused on many different operative technique modifications and the increasing use of applied fibrin glue and topical sealants for prevention of postoperative pancreatic fistula. One example of a technical modification combines the use of a vascular pedicle round ligament flap from the anterior abdominal wall to reinforce the pancreaticoenteric anastomosis in pancreaticoduodenectomy or at the stump of the pancreas following distal pancreatectomy with fibrin glue sealant [34]. From our own experience, this technique yields low rates of POPF, 8.8 % following pancreaticoduodenectomy and 5.3 % for all pancreas resection procedures [34].

From the preclinical literature, investigation was undertaken to determine the effects of biocompatibility and adhesive properties of six commercially available tissue adhesives, three cyanoacrylate derivatives, two human fibrin sealants, and one albumin glutaraldehyde [35]. While satisfactory adhesive properties were observed in animal models of pancreaticoenteric anastomosis in four of six studied tissue adhesives, all tissue adhesives studied induced histologic changes in the pancreas, which were interpreted as being potentially harmful to the pancreas [35].

In a review series of 14 articles describing the use of fibrin sealants for reduction of pancreatic fistula after distal

pancreatectomy, Wilson and colleagues conclude "that the application of fibrin glue to the pancreatic stump could help to reduce the incidence of troublesome pancreatic fistulas" [10]. The largest prospective randomized controlled trial reviewed in this series was from Suzuki et al. and found a significantly lower pancreatic fistula rate after application of TISSEEL fibrin sealant ($p=0.04$) [36]. Three other prospective randomized controlled trials found no significant difference in postoperative pancreatic fistula rates when fibrin sealants were applied after distal pancreatectomy [37–39] (Table 3).

A second review series published in 2014 included pooled data from 7 randomized controlled trials and 897 patients [40]. In this review, a trend was seen towards the reduction of postoperative hemorrhage and intra-abdominal fluid collection in those patients who received fibrin sealants; however, there was no significant difference in rates of POPF [40]. Fingerhut and colleagues conclude similar findings from their review of 24 studies including 6 randomized controlled trials of fibrin sealants in pancreatic surgery [39]. Of three trials which the authors assigned a level of evidence of 2 based upon good experimental trial design with randomization from the Cook definition [41], only the Suzuki trial found a reduction in POPF rates with application of fibrin sealant [36]; studies by D'Andrea and Lillemoe found no significant difference in rates of POPF with application of fibrin glue [37, 42]. Similar small case series and prospective randomized trials have also failed to demonstrate improvement in POPF rates following the application of the glutaraldehyde-based BioGlue, carrier-based fibrin patch TachoSil, fibrin glue plus falciform ligament patch, or fibrin sealant TISSEEL to pancreaticoenteric anastomoses and cut pancreatic surface margins [43–46].

Multiple small case series have been reported, however, in which the application of fibrin sealants or combination type sealants have demonstrated improved rates of postoperative pancreatic fistula following technique modification with fibrin-based sealant. Ochiai et al. describe the reduction of POPF following the application of polyethylene glycolic acid felt with fibrin glue to pancreaticojejunostomy site following pancreaticoduodenectomy and the cut stump following distal pancreatectomy [47]. Conaglen and Collier report a series of 30 patients in which none developed POPF following the application of fibrin glue to pancreaticogastrostomy anastomosis [48]. Another additional series reports successful reduction of POPF rates with application of carrier-bound fibrin adhesive to distal pancreatectomy cut surfaces [49]. Ultimately, the use of fibrin-based products or tissue sealants in pancreatic surgery likely remains a choice for surgeons based on clinical experience and individual clinical outcomes. Similar to the literature published regarding the application of fibrin sealants in liver surgery, hemostatic efficacy has been established in the realm of pancreatic surgery, but overall effectiveness in regard to tissue sealing and prevention of POPF remains debated.

Conclusions

The increasing complexity of hepatobiliary and pancreas surgery will likely continue to drive the development of biomaterials to improve outcomes and reduce both postoperative morbidity and mortality rates. Particularly with the push of minimally invasive surgical techniques gaining new ground in the realm of HPB surgery, fibrin sealants and topical agents will, in all likelihood, continue to have a place in the ease of achieving hemostasis in the operating room and potentially preventing postoperative complications. While some of the data for these agents demonstrates no significant difference to the non-use of these products and good surgical techniques, many surgeons remain comfortable with their application, and for all intents and purposes will continue to use these agents as an adjunct in their surgical practice. The effective evaluation of these products and their applicability in the realm of HPB surgery requires careful clinical trial design and thoughtful evaluation of the literature as to their effectiveness. Ultimately, in a time of exploding healthcare expenditure, the conscientious surgeon will take effectiveness, ease of use, and overall benefit to the patient when considering fibrin sealants and other topical agents in HPB surgery practice.

Conflicts of interest None.

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