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# Use of Biosurgicals in Hepatobiliary Surgery

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## Abstract

Through innovative technologies and refinement of surgical technique over the last several decades, hepatopancreatobiliary (HPB) surgeries have become increasingly common for both malignant and benign disease. HPB surgeries often present unique challenges even for the experienced surgeon, whether due to liver cirrhosis causing portal hypertension and impairment of natural clotting abilities or a large pancreatic mass invading into nearby mesenteric vessels. Major intraoperative blood loss is still a concern and is known to be a major factor influencing morbidity and mortality. Biosurgicals are increasingly used as adjuncts to reduce blood loss during these complex procedures, but also to even reduce rates of biliary and pancreatic leaks and fistulas postoperatively. While initially biosurgical agents offered some hope to make the difference in completing a safe and effective operation, more recent and rigorous studies have failed to demonstrate reproducible benefits. This chapter reviews the use of hemostatic agents in the setting of hepatobiliary and pancreatic surgery, including for the maintenance of hemostasis and the prevention of biliary and pancreatic leaks. We also discuss what factors should be considered when choosing the correct agents for different clinical scenarios during HPB surgery.

**Keywords:** hemostasis, hemostatic agent, biosurgical, hepatic surgery, pancreatic surgery, hepatobiliary surgery

## 1. Introduction

Hepatobiliary surgery has increased in frequency throughout the United States and the rest of the world over the past several decades. What was once only performed in select specialized centers is now routinely accomplished with equivalent outcomes in regional hospitals throughout the world. Even transplantations, extensive en bloc pancreatic surgeries, and major hepatic resections involving multiple liver segments are now performed regularly at high volume centers with little blood loss. This is in part due to increased incidence of pancreatic and hepatic malignancies requiring resection along with innovations and improvements of surgical technique such that patients once considered inoperable are now able to successfully undergo extensive surgery. Pancreatic cancer especially has seen increasing incidence over time, with nearly 50,000 new cases of pancreatic cancer diagnosed in 2016, compared to less than 30,000 in 1999 [1]. Additionally, as other types of cancer patients such as colorectal and breast enjoy increased overall survival with improved adjuvant therapies, the likelihood that these patients will live long enough to eventually develop recurrent or metastatic disease increases as well. Greater than

50% of all colorectal cancer patients will eventually develop hepatic metastases [2]. Given that colorectal cancer alone accounts for nearly 150,000 new cancer cases yearly in the United States [1], this quickly adds up to a significant number of patients that have the potential to receive and benefit from hepatic resection or transplantation.

Fortunately, both morbidity and mortality have significantly decreased over the years as the number of hepatobiliary and pancreatic surgeries have increased. A number of reasons can explain the observed improved outcomes, from better patient selection, to pre- and perioperative optimization, to modification and refinement of surgical technique. Certainly one important factor relating to surgical technique has been the ability to perform these major and often prolonged surgeries with minimal blood loss and frequently without the need for blood transfusion. Hepatobiliary and pancreatic surgeries especially are at risk for major blood loss. This is due to multiple factors including substantial vascularity of the organs involved, close proximity to important major vascular structures that typically must be preserved, and concomitant pathologies such as cirrhosis and/or portal hypertension that predispose the patient to increased blood loss. Minimizing blood loss remains important as blood loss and blood transfusions have been shown to be associated with increased morbidity and mortality in these procedures [3–6]. However, only fairly recently have most HPB surgeries been routinely performed without significant blood loss and transfusion requirements [7].

Whole industries have dedicated themselves to helping the surgeon minimize blood loss during an operation, and the modern operating theater is typically filled with not only the clamps and sutures of old, but also energy devices, staplers, and an increasing array of topical agents used to assist in hemostasis. Biosurgical agents have now become an increasingly available tool to the surgeon in creating and maintaining hemostasis. There are a multitude of different agents available, from physical agents that primarily provide a scaffolding for the platelet plug to form, to biologically active agents which have added thrombin, fibrin, or other components of the coagulation cascade to aid in clotting, to a combination of both. As the technology and availability rapidly grows, it can be challenging for the surgeon to decide which particular agents can or should be used in a given situation. Every surgeon should be aware of the unique aspects of HPB surgery in order to properly evaluate how

Location	Situation	Challenge	Suggested biosurgical use
Liver	Irregular surface area after injury or resection	Difficulty to visualize bleeding or applying manual pressure	Liquid agents such as fibrin or thrombin
Liver	Extensive fatty liver disease	Difficulty for parenchyma to hold sutures	Physical agents such as collagen fleece to aid hemostasis and tamponade
Liver	Cirrhosis or fibrosis	Increased bleeding due to decreased natural clotting ability	Bioactive hemostatic agents to deliver thrombin and/or fibrin to the tissue
Pancreas	Pancreatitis	Obscured tissue planes, friable tissues	Physical agents or combination agents to apply pressure
Pancreas	Vessel reconstruction	High risk of bleeding, tendency to bleed at suture line	Fibrin glues to aid hemostasis at vascular anastomosis site

**Table 1.**  
*Biosurgical agents for specific situations IN HPB surgery.*

biosurgicals may be able to aid in reduction and prevention of blood loss and other complications. Specific circumstances encountered during hepatic and pancreatic surgery may require different solutions that can be aided by biosurgicals (**Table 1**).

We would like to be clear that use of biosurgicals, especially in hepatobiliary surgery, is no substitute for good perioperative management and surgical technique. The greatest ability to maintain adequate hemostasis will always be from performance of proper basic surgical principles in a thorough and methodical fashion. However even despite significant experience, rigorous technique, and best efforts, hepatobiliary and general surgeons may find themselves in situations where bleeding is difficult to visualize, access, control, or a combination of all three. In these scenarios biosurgicals represent another tool for the surgeon to utilize in order to perform safe and effective surgery.

## 2. Hepatic surgery

Although it appears easily accessible and readily visible during any standard laparotomy, the liver can still be a challenging organ to operate on. The liver has a dual blood supply, receiving inflow from both the hepatic artery as well as the portal vein. Together these vessels channel vast amounts of blood through the liver. The liver receives 25% of the total cardiac output, despite only being typically 2.5% of the body weight. In a normal adult, this means that the total liver blood flow will range from 800 to 1200 ml/min [8]! Even small areas of injured parenchyma may lose a significant amount of blood if not identified and controlled due to the large volumes of blood flowing through the liver. During a major liver resection, large surface areas of the parenchyma may be cut and exposed at one time, which only increases the opportunity for blood loss.

The voluminous and rapid flow of blood through the liver is not the only reason for a significant opportunity for blood loss during hepatic surgery, however. The hepatic parenchyma, the primary substance of the liver made up of hepatocytes, can be quite challenging to work with and achieve hemostasis. Any hepatobiliary surgeon can tell you the challenges – or even futility – of trying to clip or suture directly to liver parenchyma. Suture material will often slide through this soft tissue, often doing more damage and causing more bleeding. Whenever feasible sutures should incorporate the Glissonean capsule of the liver which generally has much more strength to hold a suture in place, but this is not always possible. Additionally, liver injury or transection may leave behind an irregular and uneven parenchymal surface, limiting the ability to access the bleeding point or to even apply manual pressure in an effective manner. Adding to the difficulty is the fact that the majority of the vascular and biliary anatomy lies hidden within the hepatic parenchyma, and is not readily visible without ultrasound or fluoroscopic guidance. Therefore, the surgeon should take care when placing a suture or even stapler into the liver to stop bleeding lest an even larger vessel or bile duct that resides nearby sustain injury.

An additional complicating factor in hepatic surgery involves the variability of hepatic anatomy. Nowhere else in the human body is there such variability for such major vascular and anatomic structures. Even a strong background and knowledge of common anatomical relationships will not always adequately prepare the surgeon. Nearly half of all patients will present with some form of vascular anomaly of the hepatic artery alone [9]. When also considering the bile ducts, portal veins, and hepatic veins, it can sometimes feel like every patient encountered has some form of anomaly. This becomes even more complex when considering that much

of the vasculature of the liver is not readily visible but is concealed within the liver parenchyma as noted above.

All of the considerations that have been raised thus far generally concern a patient with a normal healthy liver. Unfortunately, a large portion of patients who need hepatic surgery have significantly diseased livers. While traditionally this has meant cirrhosis and fibrosis with the possibility of portal hypertension, fatty liver disease and liver steatosis are also becoming increasingly common. The intrinsic function of the liver is intimately tied to hemostasis, as the liver is responsible for synthesizing and circulating most of the body's coagulation factors and inhibitors. A patient with liver disease, whether acute or chronic, will often have an interference of this ability to create clotting factors, which can range from mild to severe and life-threatening. While the etiology of the liver disease may vary from patient to patient, they will generally share the same hemostatic pattern. Often a patient with advanced liver disease will have significantly decreased levels of nearly all proteins that promote or inhibit coagulation, fibrinolysis, and platelet function [10]. Adding to the challenge is not only that the traditional markers of coagulopathy, prothrombin time (PT) and activated partial thromboplastin time (APTT), cannot always accurately predict the risk of bleeding in these patients, but the traditional treatment of bleeding (blood transfusions) may not always help and can potentially be harmful in this subset of patients [10].

Hepatic surgery has become much more commonplace for a variety of reasons, but certainly improvements in surgical instruments and operative technique have played an important role. As previously discussed, a major driver of morbidity and mortality in liver surgery is blood loss and blood transfusions, and therefore any attempt to decrease postoperative bleeding is of interest to hepatic surgeons and researchers. Certain innovations such as maintaining low intraoperative CVP and creating total hepatic inflow occlusion have significantly improved outcomes for even aggressive hepatic resections [11]. Further advances to continue to reduce morbidity and mortality are constantly sought after.

Biosurgicals have been studied for use in hepatic surgery since their inception. Both non-active physical agents as well as biologically active agents have been tested and evaluated. Briefly, physical agents tend to promote hemostasis by stimulating platelets and the extrinsic pathway and by providing a scaffold for thrombus deposition. A dry matrix can also act to absorb water, concentrate hemostatic factors at the site of bleeding, and exert a tamponade effect on the vessel by direct pressure. Biologically active agents on the other hand mimic endogenous coagulation, typically by directly introducing thrombin or fibrin topically to the site of bleeding.

When choosing a hemostatic agent during hepatobiliary surgery, the unique characteristics of the operative field and associated organs or structures need to be taken into consideration. These characteristics will not only determine the type of hemostatic agent used (physical agent, biologically active agent, or combination), but also the delivery method (solid sheets, powder, liquid, etc.). Each unique situation may require a different solution, and the surgeon must be flexible.

As noted earlier, the hepatic parenchyma can pose a challenge for hemostatic control for multiple reasons. After a major liver resection, there may be a large surface area that is bleeding and requires attention. Additionally, the parenchyma may be irregular and have deep holes that are not easily accessible. Biologic agents such as fibrin sealants, which typically come in liquid form, can be preferred due to the ability to quickly deliver the agent over a large area so long as the bleeding is not brisk enough to dilute it too quickly [12]. However, using liquid agents accompanied by direct pressure may be problematic as they may be absorbed by a sponge or conversely if the sponge itself is damp with thrombin then this can provide for both coagulative and absorptive functions [12]. A solid physical agent such as collagen

matrix or oxidized cellulose may be preferred for use over a smaller or uniform area where direct pressure can be applied.

Besides fibrin, topical thrombin has also been used as an adjunct for hemostasis in hepatic resection, available as bovine thrombin, human plasma-derived thrombin, and recombinant human thrombin. It is one of the most used products available and has been accessible for decades; in fact bovine thrombin was in widespread use before it was even FDA approved 60 years ago [13]. However, bovine thrombin does carry the risk of antibody formation that can result in massive hemorrhage, anaphylaxis, and even death, as well as the risk of viral transmission [14]. The development of recombinant thrombin allowed for a product that had only minimal risk of antibody formation and also free from virus risk [14]. The other alternative is human thrombin, derived from human plasma donors, which carries similar risk of blood borne pathogens as blood products as it undergoes similar testing and filtration processes [14]. The ideal formulation of thrombin for hepatic surgery has yet to be discovered, but animal models of liver injury have shown superiority of smooth gelatin-thrombin hemostats in the ability to retain thrombin, and less intraoperative blood loss when compared to a stellate gelatin-thrombin hemostat [15].

Biosurgicals have primarily been investigated for two purposes in hepatobiliary surgery: maintenance of hemostasis and prevention of bile leak.

## **2.1 Preventing and maintaining hemostasis in hepatic surgery**

Various agents for postoperative hemorrhage control have been studied and used in practice, but have mixed results in the literature. Animal models were first used to evaluate biosurgicals for hemostasis. In one case control study of liver injury in rat models, hot air coagulation, fibrin sealant, and suture hepatorrhaphy with horizontal mattress sutures were compared [16]. Data supported fibrin sealant to be the superior technique of the three considering it was very effective at achieving hemostasis and allowed the liver to return to its normal shape and more quickly regenerate [16]. There were some notable drawbacks however, including risk of abscess formation which was found to be higher than the hot air group but lower than suture technique. Other considerations included the high cost and prolonged preparation time, although both have improved significantly since this study was performed.

A series of important clinical studies of hemostatic agents in liver surgery have taken place over the past several decades. Fibrin sealants showed initial promise for providing hemostasis in the setting of major liver resection. The liquid form allows for sprayed fibrin sealant to be applied over a large cut surface area and easily gain access to any irregular grooves or cuts within the parenchyma itself. While fibrin sealant has consistently demonstrated effectiveness in regards to time to hemostasis during surgery, or percentage of cases with complete hemostasis after a designated time, these results rarely have translated to improved clinical outcomes. Randomized controlled trials have unfortunately failed to show a reduction in clinically important outcomes such as intraoperative blood loss, intra- or postoperative transfusion requirements, or bleeding episodes postoperatively [17–21]. Similarly disappointing results have been seen with a combination of bovine collagen and thrombin mixed then sprayed over the surgical bed [22]. Physical agents generally fare no better, as fibrin sealant has been shown to be roughly equivalent in terms of clinical outcomes when compared to either collagen powder or cellulose sheets in hepatic resections [23, 24].

Newer studies have evaluated a combination of collagen and coagulation factors, typically in the form of a so-called carrier-bound collagen sponge coated with fibrinogen and thrombin, commonly marketed as either Tachocomb or

Tachosil. Briceno et al. conducted a prospective, controlled, quasiexperimental study comparing the effectiveness of utilizing a ready-made coated collagen sponge (Tachosil) compared to no sponge in patients undergoing hepatectomy [25]. This study was probably the most favorable toward biosurgicals, as it demonstrated not only decreased transfusion requirements in the collagen sponge group, but also decreased mean hospital stay, moderate to severe postoperative complications, and drainage volume after collagen sponge use [25]. Notably these results were more prominent in the major hepatectomy subgroup, rather than those patients who underwent minor liver resections. Unfortunately while the aforementioned carrier-bound collagen sponge appears to have abundant references in the literature, these impressive results have not been easily reproduced. Additional studies have failed to confirm significant improvement in intraoperative blood loss, intra- or postoperative transfusion requirements, clinically significant postoperative fluid collections, bleeding complications, or mortality when compared to control groups using argon beam coagulation or even other single agent biosurgicals such as plain oxidized regenerated cellulose [26–29]. Also interesting is that although nearly all studies demonstrate decreased time to hemostasis using these hemostatic agents, when explicitly measured the total operative time has actually been shown to be increased in this group [17]. Most recently Kobayashi et al. have tried to show further improvement with the use of a fibrin sealant and polyglycolic acid felt in a randomized controlled trial. When compared to a carrier-bound collagen sponge used during hepatic surgery, the fibrin sealant group had reduced overall morbidity, infection, jaundice, and abdominal paracentesis rates, but of note was that the rates of hemorrhage were similar between the two groups [30]. Further studies are needed to confirm these early results for this novel agent combination.

Despite a lack of good quality and reproducible data demonstrating clinical effectiveness, biosurgicals are still widely used. This is likely due to anecdotal evidence, positive personal experience, or even word of mouth. Surgeons are using these agents not only to reduce bleeding during hepatic surgery, but for a host of other reasons. A Dutch national survey showed that topical agents were used by nearly 90% of surgeons during hepatic resection, with fibrin sealants being the most commonly used [31]. Surgeons reported using these agents to shorten time to hemostasis but also to reduce resection surface related complications such as postoperative hemorrhage, abscess formation, and bile leak [31]. A more recent survey of UK hepatobiliary specialists also revealed that a majority of surgeons (62%) admitted to using hemostatic adjuncts “routinely” during liver surgery while the remainder used them occasionally [32].

The best type of agent to assist hemostasis after hepatic resection is still not known. Increasing need for and performance of hepatic surgery will likely continue to drive use of any agents thought to reduce complications in these complicated and dangerous surgeries. At this time however, no specific agent can be recommend for routine use to reduce postoperative bleeding during hepatic surgery, and further studies still need to be conducted.

## **2.2 Preventing biliary leak/fistula**

While thrombin products can be used to catalyze many reactions in the blood clotting cascade, the end product of arguably the most important reaction is a fibrin lattice or clot. Fibrin in the form of a sealant, often in conjunction with thrombin, is readily used in hepatobiliary surgery and not just for hemostatic purposes. Biosurgicals have also been evaluated for use in preventing a troublesome complication after hepatobiliary surgery – bile leak. However, proper evaluation of the literature on this subject is challenging because there has only recently been an

accepted consensus definition and grading of severity for bile leakage after hepatobiliary surgery [33].

Initial studies in animal models examining the use of biosurgicals for prevention of biliary leak appeared promising. Biosurgical sealants were shown to be effective in reducing drain output and rate of bile leakage in pig models of purposely incomplete end-to-end choledochocholedochostomy [34]. However clinical trials on humans have not demonstrated similarly positive outcomes. Several recent systematic reviews and meta-analyses have failed to demonstrate significant reduction in biliary leakage rates with the use of fibrin sealants or other topical agents used intraoperatively compared to standard treatments [35, 36]. The lack of conclusive results may at least be partially due to the heterogeneity among the current literature and failure of a standardized definition of bile leak until only recently. Further well-designed randomized controlled trials utilizing the current consensus definitions are necessary to clarify if any agents may be beneficial for preventing biliary leakage after liver resection.

### **3. Pancreatic surgery**

The pancreas has long been an organ considered off limits to most surgeons in routine surgical situations. Its location deep within the abdomen, proximity to major vascular structures, and soft parenchyma have given it a reputation for being an unforgiving organ in surgery. As not only surgical technique but also anesthesia and critical care management have evolved over time, even extensive pancreatic resections are now undertaken on a regular basis. The need for pancreatic surgeries is expected to increase in the United States as the number of pancreatic cancers continues to rise [37]. These two factors in combination are expected to result in a dramatic rise in the number of pancreatic surgeries performed in the coming years.

The primary difficulties that the surgeon must overcome when operating on the pancreas include maintaining adequate hemostasis without simultaneously injuring the pancreatic parenchyma, pancreatic duct, and/or surrounding vascular structures and avoiding pancreatic leak and fistula formation. Pancreatitis may complicate any operation on the pancreas by obliterating the typical tissue planes around the pancreas, and the resultant inflammation may make the friable tissues bleed more easily. Additionally, in the setting of large pancreatic or duodenal tumors, the surgeon may be required to resect and reconstruct nearby veins or arteries in order to complete an appropriate oncologic resection with negative margins. Unfortunately, these challenges are often interrelated and may all occur in the same patient. Pancreatic cancer is known to be pro-inflammatory and is often associated with inflammation and pancreatitis changes. Large en bloc resections may require major vascular resections and can result in more severe intraoperative blood loss, while increased blood loss has been implicated in postoperative pancreatic fistula formation [38, 39].

Biosurgicals for use in pancreatic surgery have continued to gain in popularity, especially as more agents become readily available. Blood loss during pancreatic surgery is common and often voluminous. As an example, an amount of blood loss <400 ml during a pancreaticoduodenectomy falls into the lowest risk category for pancreatic fistula risk scoring systems, and blood loss in the 700–1000 ml range is common [39]. Blood loss in the setting of pancreatitis, both acute and chronic, can be even more severe as the inflamed tissues may bleed much more easily and major vascular structures cannot be as readily identified and preserved. Therefore, any strategies to reduce hemorrhage are welcomed by HPB surgeons.

While biosurgicals can be used to aid hemostasis just as in any other operation, significant interest has also been shown in the possibility that these agents could also help reduce the incidence or severity of pancreatic leaks and pancreatic fistulas

postoperatively. Despite advances in surgical technique and the availability of a multitude of advanced clips, staplers, and other adjuncts, the pancreatic fistula rate after pancreatic surgery remains high, with reports often 20% or more [38]. The very nature of many hemostatic agents as “glues” or “sealants” has led to investigating their effectiveness in prevention of pancreatic fistula formation. As long as pancreatic surgery remains technically challenging and fraught with potential complications, surgeons will be eager to adopt new methods and new agents. Biosurgicals offer significant potential to aid the surgeon and patient toward better outcomes in pancreatic surgery.

### 3.1 Preventing and maintaining hemostasis in pancreatic surgery

The pancreas has a robust vascular supply and is in close proximity to several major named vascular structures, thus significant bleeding during pancreatic surgery can be common. This bleeding typically takes two forms: hemorrhage from the pancreatic parenchyma or bleeding from surrounding vascular structures such as portal vein, superior mesenteric vein, superior mesenteric artery, gastroduodenal artery, or any of their major branches. However, few studies have specifically evaluated the use of hemostatic agents in preventing or reducing bleeding during pancreatic surgery. Reports of the use of collagenic fleece to aid hemostasis in pancreatectomy and in the retroperitoneum after pancreatic resection have been reported with favorable results [40] but no rigorous prospective randomized controlled trials have evaluated their hemostatic effects in this specific situation to date.

While biosurgical agents are generally effective at reducing blood loss and obtaining and maintaining hemostasis for major abdominal surgery, the efficacy is often related to the type of surgery. While there is a strong likelihood that hemostatic agents are effective in assisting the surgeon to maintain hemostasis in pancreatic surgery, there is no data to support or refute those claims. Until specific studies are done in the setting of pancreatic surgery, we cannot specifically recommend any specific one biosurgical agent over another to reduce blood loss or transfusion requirements in these patients.

#### 3.1.1 Graft bleeding (after venous resection/reconstruction)

As previously described, it has been established that excessive blood loss correlates with higher risk of fistula formation among other postoperative complications [38, 39]. One of the sources of increased blood loss during pancreatic surgery, especially pancreatoduodenectomy, can be during venous reconstruction. Although initially controversial, vein resection is now the standard practice if the surgeon deems it necessary in order to achieve an R0 resection. This practice is currently recommended by most major surgical societies and are a part of the National Comprehensive Cancer Network (NCCN) guidelines [41, 42]. The ideal method of reconstruction is still not yet known but several options can be considered depending on the clinical situation and anatomy including primary end-to-end anastomosis, autologous interposition grafts (from internal jugular, saphenous, superficial femoral, gonadal, or external iliac veins), synthetic grafts (such as PTFE or bovine pericardium), or cadaveric allograft [43, 44]. As with any other vascular anastomosis, bleeding from suture lines can put the anastomosis at risk as well as prolong operative time. Thus, hemostatic agents can be effective here as well. Fibrin glues and other surgical sealants have shown significantly decreased bleeding time in vascular anastomoses compared to manual compression alone [45, 46]. Given this favorable data, it would be worthy of consideration to use these products for anastomoses with the goal of decreasing blood loss and operative time.

### 3.2 Preventing pancreatic leak/fistula

As mentioned previously, biosurgicals have gained more widespread use in hepatobiliary surgery not just for their hemostatic properties alone. Postoperative pancreatic leaks and fistulas unfortunately remain common after pancreatic resection, and have the potential to significantly increase morbidity and even lead to mortality. Physical and biologic hemostatic agents are just the new wave of products that have peaked surgeons' interest in preventing this morbid complication. Multiple attempts have been made to alter surgical technique, such as stapling, over-sewing the transection line, and main duct ligation to name a few. However no one technique has demonstrated reproducible and superior outcomes for reducing pancreatic fistula rates. Surgeons have now increasingly turned to adjunctive agents to assist in the avoidance of postoperative pancreatic fistula formation.

Evaluating interventions for pancreatic fistula formation are challenging for several reasons. Postoperative pancreatic fistulas can have a wide range of severity. While some pancreatic leaks remain asymptomatic and are only detected biochemically, others cause severe clinical consequences requiring intervention and possibly resulting in sepsis and even death. Although pancreatic fistulas have been extensively studied and a large body of literature is dedicated to the subject, there has remained a lack of standardization of the definition of pancreatic fistula until only recently. In 2005 the International Study Group on Pancreatic Fistula (ISGPF) released a consensus definition and grading system of postoperative pancreatic fistula [47]. This was revised recently in 2017 and is now defined as "a drain output of any measurable volume of fluid with an amylase level  $>3$  times the upper limit of institutional normal serum amylase activity, associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula" [48]. Prior to these guidelines being published, many studies suffered from non-standard and differing definitions of pancreatic fistula and it was challenging to compare studies published from different institutions.

Fibrin sealants have been some of the first agents evaluated for pancreatic fistula prevention, first in the setting of distal pancreatectomy. In one of the earliest reported studies, Suzuki et al. demonstrated significantly decreased postoperative pancreatic fistula formation in a randomized controlled trial evaluating the use of fibrin glue on the suture line of the pancreatic stump during distal pancreatectomy for pancreatic and gastric cancer [49]. The pancreatic fistula rate was shown to decrease from 40% in the control group to 15.4% in the fibrin glue group. Several subsequent studies further demonstrated that fibrin glue may be used to reduce the rate of pancreatic fistula formation [50, 51]. However, as discussed above, many studies were flawed from a lack of standard definition of pancreatic fistula, and results are difficult to extrapolate to modern times. Additional and more recent prospective trials evaluating fibrin glue in the setting of distal pancreatectomy have failed to support their ability to reduce pancreatic fistulas [52, 53]. Other attempts to inject fibrin glue directly into the main pancreatic duct in order to reduce fistula formation have similarly failed to show promise in improving outcomes [54]. A recent systematic review and meta-analysis as well as a recent Cochrane review have both concluded that based on the current available evidence, fibrin sealants likely have little to no effect on postoperative pancreatic fistula formation in patients undergoing distal pancreatectomy [55, 56].

Fibrin glue has also been evaluated as an adjunct to reinforce the pancreatic anastomosis after pancreaticoduodenectomy. Pancreatic fistulas in this setting, while slightly less common than after a distal pancreatectomy, can still cause significant morbidity. A major prospective randomized trial at Johns Hopkins sought to answer if fibrin glue may reduce postoperative pancreatic fistula formation after Whipple procedure [57]. While patients were only enrolled in the study

if the surgeon determined that the patient was at risk for pancreatic fistula (i.e. soft parenchyma and non-dilated pancreatic duct), one strength of this study was that surgical technique was controlled for and standardized. The treatment group had 8 mL of fibrin glue applied to all three anastomoses while the control group had none. The rate of all pancreatic fistulas (both clinically relevant and silent) were 26% in the treatment group and 30% in the control group; there was also no difference in overall complications, yielding the conclusion that application of fibrin glue provides no benefit [57]. While several retrospective or single arm observational studies have shown promise [58, 59], further prospective studies have failed to demonstrate significant benefits to using fibrin glue during Whipple procedure [60, 61]. A Cochrane review on the subject could not conclude whether fibrin sealants were beneficial in the setting of pancreaticoduodenectomy, although the number and quality of studies are significantly less than those for distal pancreatectomy [55].

In addition to single agents such as fibrin, multi-agent compositions such as a carrier-bound collagen sponge coated with fibrinogen and thrombin have also received significant attention. These agents whether marketed as TachoComb or the newer product without added aprotinin and human (instead of bovine) thrombin known as TachoSil, but both appear to have similar efficacy [62]. A recent observational study comparing carrier-bound collagen sponge coated with fibrinogen and thrombin compared to both polyglycolic acid sheet only and a control group with no biologics did show a significantly decreased rate of clinically relevant (grade B or C) postoperative pancreatic fistula formation with the use of either of the two biosurgicals [63]. Unfortunately these results have not been further supported in rigorous prospective randomized controlled trials.

One of the first prospective studies to evaluate the effectiveness of these agents was a multicenter study in Italy evaluating patients undergoing distal pancreatectomy [64]. Patients were randomized to receive collagen sponge coated with fibrinogen and thrombin at the resection line or no reinforcement to the resection line. There was no standardization regarding surgical technique (surgeries were performed laparoscopic or open, by stapling or suturing of the pancreatic margin, and with or without spleen preservation). While there was a reduction in drain amylase level on postoperative day #1 in the collagen sponge group, the rates of clinically relevant pancreatic fistulas were similar between the two groups as were length of days until drain removal and length of hospital stay [64]. A more recent multicenter prospective randomized French study had similar outcomes, where patients were randomized into either carrier-bound collagen sponge coated with fibrinogen and thrombin group or control group. While operative technique was not controlled, the technique for placing the sealant on the suture line was (overlap of 2.5 cm and direct pressure held for 3 min), and ISGPF definitions were used. Results of this trial demonstrated no statistically significant difference in the incidence of overall POPF (all grades) or in clinically relevant fistulas; the Tachosil group had an overall POPF rate of 54.5% and the control group a rate of 56.6% [65]. An additional multicenter randomized controlled Japanese study also failed to exhibit decreased fistula rates using a collagen sponge coated with fibrinogen and thrombin, demonstrating similar rates of overall POPF, including clinically relevant grade B and C fistulas [66]. The strengths of this study included uniform surgical technique (stapling of pancreas), rigorous criteria for the definition of pancreatic fistula according to the ISGPF guidelines, and a majority of surgeries were performed laparoscopically.

While promising and theoretically useful, at this time no conclusive evidence supports the use of biosurgicals for preventing pancreatic fistulas. The most robust data involve either fibrin glue or collagen sponge with fibrinogen and thrombin. The ideal agent or optimal method of application has not yet been discovered, and further studies are required to prove benefit at this time.

## 4. Conclusions

In few other areas of surgery is the potential for and consequences of blood loss so great as in hepatobiliary and pancreatic surgery. It is clear to see why substantial time and resources have been put into finding adjuncts to obtaining and maintaining hemostasis in hepatic surgery. Not surprisingly, biosurgical agents have been used and evaluated during these procedures since their early introduction and adoption. While initial animal models often showed great promise in reducing intraoperative hemorrhage and postoperative bleeding complications, these benefits have generally not translated to real life clinical settings in humans. Intraoperative bleeding time and time to hemostasis are generally improved with the use of hemostatic agents in HPB surgery, but it is unclear what clinical benefits if any may be derived from those outcomes, considering total blood loss, transfusions requirements, and postoperative bleeding episodes remain generally unchanged. Similarly, rates of biliary and pancreatic leaks appear resistant to treatment with biosurgical agents as well, as leak rates do not appear to differ when these agents are used. Despite these shortcomings, most surgeons admit to using biosurgicals regularly during HPB surgery, while sharing anecdotal episodes of clinical improvements. Great promise still remains.

We are still some time away from truly “bloodless” liver surgery. With the traditional clamps and sutures, clips and cautery we were able to begin safely operating on the liver and pancreas. Through novel energy devices and titanium staplers we have made great leaps and bounds to refine these surgeries to the point where they are now routinely offered to large numbers of patients worldwide. Biosurgicals provide an opportunity to take the next leap forward in hepatobiliary surgery, potentially even increasing the safety profiles of these major complex surgeries to little more than comparable outpatient procedures.

## Conflict of interest

The authors declare no conflict of interest.

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