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ORIGINAL ARTICLE

Mechanical strength of biliary defect closure after topical sealing: Comparison of four sealants in a porcine model

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KEYWORDS
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Summary *Background/Objective:* Biliary leakage is a potential complication of liver resection and is still a concern. The aim of the present study was to evaluate the effectiveness of four routinely used sealants in preventing bile leakage under pressure from an induced perforation of the gallbladder in a porcine model.
Methods: Forty Landrace pigs were randomly assigned to one of five groups. These included a control group ($n = 8$) and one group each for the sealants TachoSil®, TissuCol Duo®, Coseal®, and FloSeal® ($n = 8$ per group). In the control group, the perforation was left unsealed. To evaluate the biliostatic potential of the sealants, we measured the pressure that was needed to induce leakage (mmHg) and the gallbladder volume (cc) at the time of leakage in each group.
Results: A significantly higher mean pressure was required to induce leakage in the sealant groups compared with the control group. However, the biliostatic effects were heterogeneous among the sealant groups. Sealants with the highest to lowest effectiveness were TachoSil, Coseal, TissuCol, and FloSeal. The mean gallbladder volume at the time of leakage also varied between sealant groups.
Conclusion: Biliostatic properties are markedly improved by the use of modern sealants compared with using no sealant. However, the advantages and disadvantages of using sealants should be carefully considered in each clinical situation. The effectiveness of the sealants should be evaluated in chronic and clinical studies.

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1. Introduction

Liver resection has become a popular treatment for localized malignant or benign lesions of the liver.[1] Advanced understanding of hepatic anatomy and physiology and improvements in perioperative care have dramatically reduced perioperative morbidity and mortality associated with liver resection.[2] Furthermore, the use of new methods (such as laparoscopic liver resection) has increased, improving the safety and outcome of hepatectomy.[3,4] However, surgeons cannot isolate and secure all small vessels and bile ducts, and it is impossible in most cases to completely eliminate blood loss and biliary leakage.[5–7] Bleeding and bile leakage are the major causes of morbidity and mortality after liver surgery.[8] Therefore, managing the raw surface of the liver remains a challenge for hepatobiliary surgeons.[2,7,9] Despite a significant decrease in overall operative morbidity, the rate of biliary complications has not changed significantly, with a reported incidence of 2.6%–8.1%.[2,10–17] Bile leakage following liver surgery can debase the quality of the postoperative course and lead to hospital death.[18]

Plasma proteins have been used as tissue sealants since 1909, when Bergel[19] controlled bleeding with dry plasma during surgery. In 1915, Grey[20] used fibrin patches as a hemostatic agent during cerebral surgery. In 1944, a combination of fibrinogen and thrombin components was used by Chronkite[21] as an adhesive agent. Commercial concentrates containing clottable fibrinogen and factor XIII became available in Europe in the late 1970s.[22] The use of fibrin sealants to prevent bleeding, bile leakage, and fluid accumulation during liver surgery is well accepted.[23–31] In addition, repeat liver resections are now more common in recurrent disease and sealants have improved the surgical outcomes.[4] However, the resistance of sealants to induced pressure in an experimental surgical setting has not been well investigated. In the present study, we assessed the effectiveness of different sealants in preventing bile leakage under pressure. Investigating the biliostatic potential of sealants on the liver surface after liver resection and intrahepatic bile system injury is practically difficult. Similarly, measuring the resistance of sealants to increasing pressure is also challenging. Therefore, we used a perforated gallbladder as a representative model to simulate intrahepatic biliary system injury.

2. Materials and methods

To evaluate the biliostatic potential of four modern, commonly-used sealants under increased pressure, a perforated gallbladder model was used to represent the intrahepatic biliary system. Data from control and sealant groups were compared.

2.1. Animal groups and experimental model

Forty Landrace pigs aged 4–6 months with body weights ranging from 25 kg to 30 kg were randomly assigned to a control group ($n = 8$) or one of four sealant groups ($n = 8$ per group). The sealant groups were TachoSil® (Takeda, Berlin, Germany), TissuCol Duo® (Baxter; Unterschleiβheim, Germany), Coseal® (Baxter; Unterschleiβheim, Germany), and FloSeal® (Baxter; Unterschleiβheim, Germany). All pigs had a healthy gallbladder and there were no signs of gallstones or other diseases. Perforations in the experimental control group were left unsealed to measure and control the pressure during experiments.

A laparotomy was performed under general anesthesia through a midline incision. Afterwards, the common bile duct and cystic duct were carefully dissected. To make the model as histologically similar as possible to the intrahepatic bile ducts, the serous layer was gently dissected and removed from the gallbladder. Afterwards, the cystic duct was catheterized using a three-way catheter that measured the pressure at the catheter tip. The catheter was then inserted into the middle of the gallbladder. A ligature was placed over the body of the cannula 1 cm from the entrance point to prevent bile from leaking back into the main hepatic duct. A 50 cc syringe was filled with a mixture of 20% bile and normal saline. Simple manual injections were performed, injecting a volume of 5 cc over 1 min (Fig. 1A).

2.2. Measured parameters

Intra-gallbladder pressure (mmHg) was recorded after each 5 ml injection into the gallbladder. The intra-gallbladder pressure (mmHg) and intra-gallbladder volume (ml) were recorded from the time of induced perforation to the onset of leaking (Fig. 1B).

2.3. Application of the sealants

To seal the induced perforation, we applied four different commercial sealants to eight pigs in each group as follows:

2.3.1. TachoSil® (fibrinogen-impregnated fleece)

TachoSil fleece was soaked in Ringer solution (room temperature) prior to application. The perforation was covered with a 1.5×1.5 cm^2 area of TachoSil and light pressure was applied to the sealant for 30 s with moist gauze (Fig. 1C). TachoSil is recommended as an adjunct to hemostasis in cardiovascular and hepatic surgery by the U.S. Food and Drug Administration (FDA).

2.3.2. TissuCol Duo® (fibrin sealant)

TissuCol Duo® was kept at room temperature for 20–30 min before application. The perforation was covered

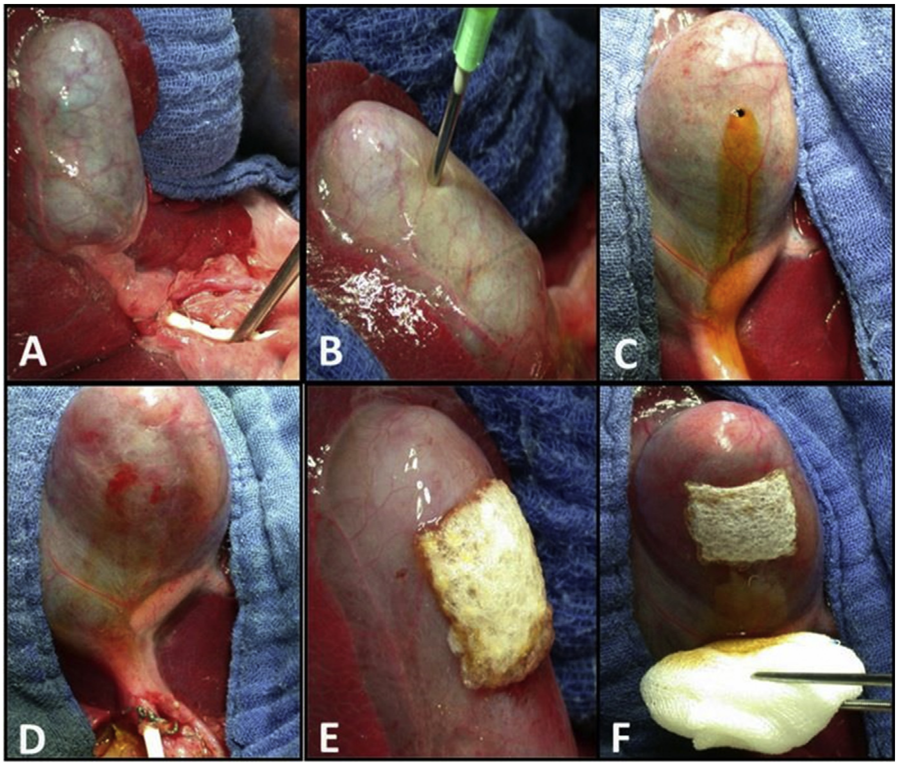

Figure 1 A: Cannulation of the gallbladder to manipulate and measure the internal pressure of the gallbladder. B: Standardized perforation of the anterior wall of the gallbladder. C: Unmanaged gallbladder perforation (control group). D: After applying Tissucol Duo E: Sealing the perforation with TachoSil prevented bile leakage. F: Increasing the intra-gallbladder pressure and bile leakage in the TachoSil group using dry gauze.

with 2 ml TissuCol Duo® using the application cannula and left for 2 min to seal the perforation (Fig. 1D). The use of TissuCol Duo® as an adjunct to hemostasis as well as an adjunct to standard surgical techniques to prevent leakage from colonic anastomoses is approved by the FDA.

2.3.3. Coseal® (hydrogel-based sealant)

Coseal has two components, which polymerize within 30 s of being combined. We combined the two components and covered the perforation with 2 ml of the Coseal® mixture. We left the Coseal® sealant for 1 min to polymerize (Fig. 1E). Coseal® is approved for use as an adjunct to hemostasis in vascular reconstructions by the FDA.

2.3.4. FloSeal® (thrombin-impregnated collagen particles)

FloSeal was prepared and 2 ml was applied to the perforated area, then fixed with mild pressure using wet gauze for 5 min. FloSeal® is approved by the FDA as an adjunct to hemostasis in surgical procedures.

2.4. Monitoring of systemic circulation

Heart rate was continuously monitored by surface electrocardiogram recording (Hellige Monitoring Station, Germany). During the experiments, systemic mean arterial pressure and central venous pressure were continuously recorded from catheters inserted into the common carotid artery and internal jugular vein, respectively.

2.5. Anesthesia protocol

All operations and subsequent investigations were performed under general anesthesia. After premedication (intramuscular injection [i.m.] of 1–2 mg azaperone), anesthesia was induced with ketamine (10 mg/kg, intravenous injection [i.v.]), midazolamine hydrochloride (0.25 mg/kg, i.v.), pancuronium bromide (0.08 mg/kg, i.v.), and continued with fentanyl (0.05 mg/kg/h, i.v.) infusion. Animals were placed on mechanical respiration (oxygen: 0.5–1 l/min, nitrous oxide/isoflurane: 1.5–2 l/min). Additionally, the pH, pO_2, pCO_2, and HCO_3 concentrations were regularly measured in arterial blood. The respiration parameters were adapted according to the blood gas analysis. During surgery, a controlled infusion of Ringer solution (20 ml/kg/h) was performed and the body temperature was measured continuously using a rectal temperature probe. During the experimental procedure, the body temperature was kept above 36 °C using heated blankets (Warm-Touch, Mallinckrodt Medical) and infrared heating lamps on the operating table.

2.6. Statistical analysis

Data were expressed as mean ± standard deviation (SD). Differences between mean values in different groups were evaluated using the Student *t*-test for paired and unpaired data and the Mann-Whitney-U test. The Chi square test was used to determine significant differences between categorical data. For all analyses, StatView 5.0 (Abacus Concept Inc., Berkley, CA, USA) was used. P-values < 0.05 were considered statistically significant.

2.7. Animal care

All animals received humane care in compliance with the National Research Council's criteria for humane care, as outlined in the *Guide for the Care and Use of Laboratory Animals* (National Institute of Health Publication 86-23, revised 1985). The study protocol was approved by the German Committee for Animal Care, Karlsruhe, Germany (approval number: 35—9185.82/A-1/12). After the experiments, all animals were sacrificed with an i.v. injection of 2 mmol/kg KCl under deep anesthesia.

3. Results

A successful biliostatic effect was defined as maintenance of sealing and no leakage at 60 mmHg. The percentage success of the four different sealants to prevent leakage decreased with increasing intraluminary pressure compared with controls (Fig. 2). The mean intra-gallbladder pressure and mean gallbladder volume at the time of bile leakage were prominently increased by the use of sealants compared with controls ($P < 0.05$) (Fig. 3). Maximum bile leakage was observed in the control group because the biliary defect was unmanaged. There were differences in the mean pressure (TachoSil, 90 mmHg; FloSeal, 46 mmHg) and gallbladder volume (TachoSil, 48 ml; FloSeal, 29 ml) between the different sealants. The use of sealants reduced bile leakage in our experimental model, but the rate of reduction depended on the type of applied sealant.

The application of sealants improved the biliostatic effect compared with controls. Biliostasis was completely insufficient (0% success rate) in the control group, where no sealant was used. The pressure needed to induce bile leakage was significantly different between all sealant groups and the control group ($P < 0.005$). Biliostatic effects were heterogeneous among the sealant groups (TachoSil, 100% success rate; TissuCol®, 57%; FloSeal, 33%; and Coseal®, 28%).

TachoSil showed the highest resistance to pressure in our experiments and was significantly better than FloSeal in preventing leakage from the perforation ($P = 0.003$). However, although higher pressure was needed to induce leakage from TachoSil-sealed perforations compared with TissuCol and Coseal, these differences were not statistically significant. TissuCol was more resistant to pressure than Coseal ($P = 0.02$), but not FloSeal ($P = 0.24$). Although FloSeal was more resistant to pressure than Coseal, this difference was not statistically significant (Fig. 4).

The gallbladder volume at the time of leakage was significantly higher in TachoSil-sealed animals compared with animals sealed with TissuCol ($P = 0.003$), FloSeal ($P = 0.002$), and Coseal ($P = 0.009$). The gallbladder volume was significantly higher in TissuCol-sealed animals than FloSeal- and Coseal-sealed pigs, but these differences were not statistically significant. There were also no significant differences in gallbladder volume between FloSeal- and Coseal-sealed animals.

4. Discussion

Liver resection is the treatment of choice for benign or malignant liver tumors and is a demanding operation in the field of hepatobiliary surgery. Bile leakage is a major complication of this procedure and raises important postoperative concerns. The aim of the present study was to evaluate the effectiveness of four different sealants in sealing an induced perforation of the gallbladder and preventing bile leakage under pressure in a porcine model. The gallbladder was assessed as a representative of the biliary system. The serous layer was removed from the gallbladder, making it more histologically similar to the intrahepatic bile ducts after resection. The adhesion and interaction of sealants with the gallbladder was partly generalized to the bile ducts and analogous structures.

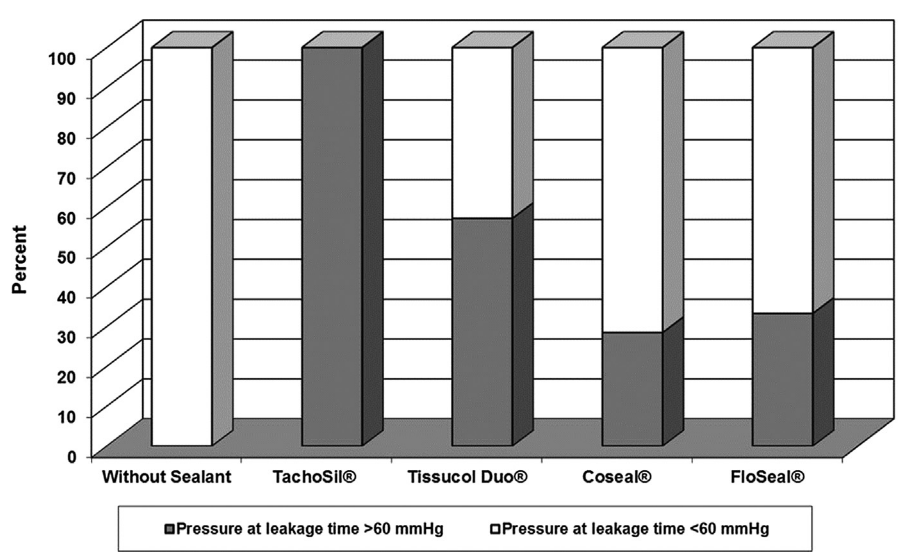

Figure 2 Percentage success of sealant resistance against high pressure.

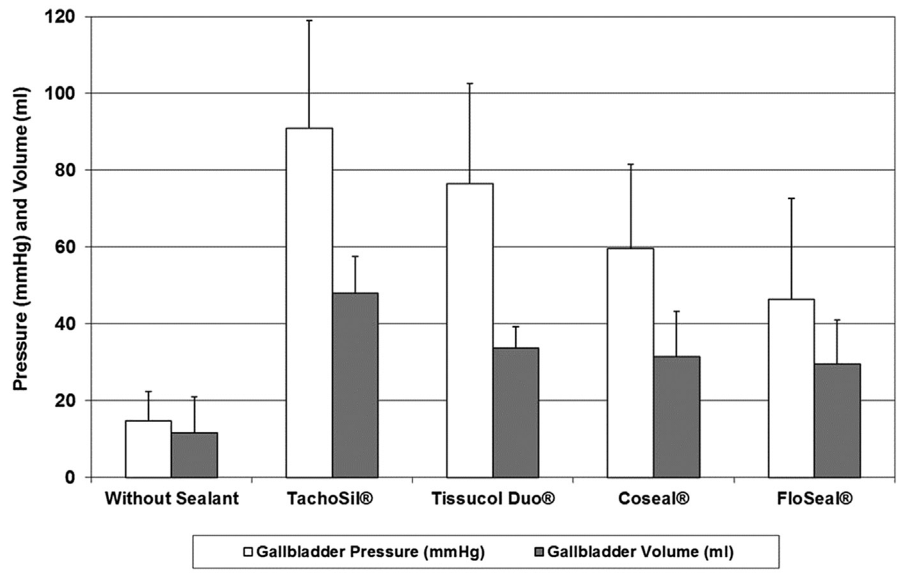

Figure 3 Mean and standard deviation of intra-gallbladder pressure and volume at the time of leakage. All sealants tolerated higher pressures than controls ($P < 0.05$).

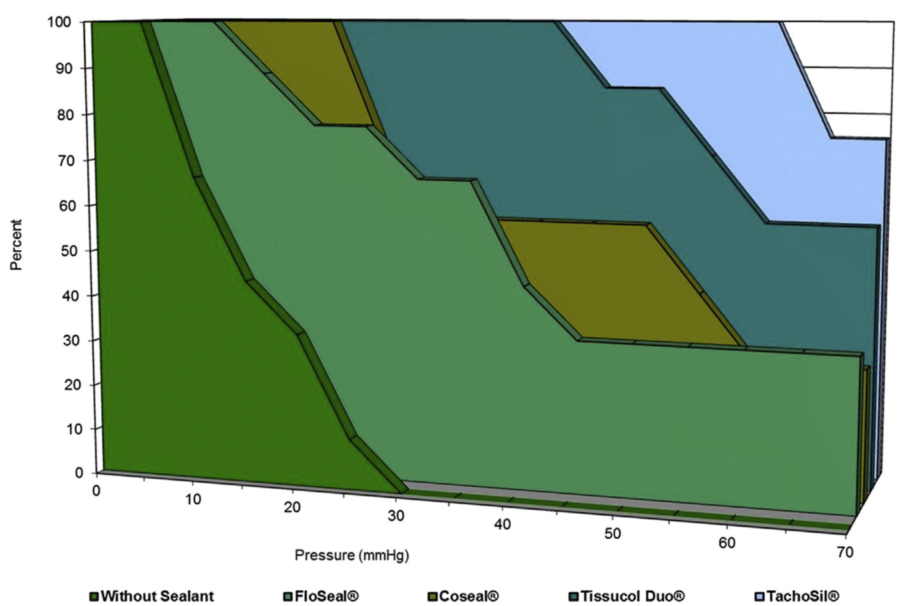

Figure 4 Resistance to pressure. TachoSil showed a stronger resistance to pressure than FloSeal and prevented leakage from the perforation, but this was not significant when compared with TissuCol and Coseal. TissuCol was significantly more resistant than Coseal but not FloSeal. FloSeal was more resistant to pressure than Coseal, but the difference was not statistically significant.

Several dressing materials have been used to prevent posthepatectomy complications such as bleeding and bile leakage. Some dressing materials, such as the Veriset™ hemostatic patch, are similar to other fibrinogen-impregnated fleeces regarding hemostasis.[32] In the present study, we used four commercial sealants to prevent bile leakage. TachoSil (fibrinogen-impregnated fleece) contains coagulatory components (fibrinogen and thrombin) on a solid, mechanically stable carrier (collagenous fleece).[33] TissuCol Duo® (fibrin sealant) is a classical fibrin glue with two components. The first component contains fibrinogen, factor XIII, plasma fibronectin, plasminogen (TissuCol-solution), and the plasmin inhibitor aprotinin. Sodium citrate, NaCl, plasminogen, glycine, human albumin, heparin, triton, creatine, and water are added as adjuvants. The second component contains thrombin and $CaCl_2$, and NaCl, glycine, and water are added as adjuvants.[34] Coseal® (hydrogel-based sealant) is a biocompatible, latex-free, synthetic hydrogel consisting of two polyethylene glycol (PEG) derivatives that are coagulation-independent. Because Coseal is not made from human blood products, the risk of viral transmission is eliminated.

The dry PEG components are dissolved in a phosphate-sodium-carbonate buffer before use, after which they polymerize within 30 s.[35] FloSeal® (thrombin-impregnated collagen particles) is a bovine-derived thrombin gelatin matrix sealant consisting of a thrombin solution combined with gelatin particles, which swell after contact with blood via the coagulation cascade.[36] The polymerization mechanism of TachoSil, TissuCol, and FloSeal is based on the coagulation cascade. The interaction of these sealants with bile and the biliary system is still not fully understood.

The present study showed that the application of sealants improved the biliostatic effect under pressure compared with the control group. The different tested sealants had different sealing effects, which may be explained by the unique components of each sealant. In our study, the intra-gallbladder pressure was artificially increased and recorded continuously until the time of leakage. The basal intra-gallbladder pressure has been reported to range from 2 to 15 mmHg.[37,38] We applied a much higher pressure to induce bile leakage in our animal experimental model. TachoSil-sealed gallbladders reached a mean pressure of 91 mmHg before leakage was induced, which was 550% more pressure than controls. TissuCol, Coseal, and FloSeal showed 450%, 436%, and 228% more resistance to leakage than controls. These findings suggest that these sealants may protect against bile leakage after hepatic resection. However, this needs to be confirmed in future studies.

Our findings are supported by previous studies. Kram et al showed that common bile duct anastomoses could be sealed with fibrin sealants in dogs[39] and concluded that fibrin sealants protect against leakage. Noun et al evaluated the biliostatic and hemostatic effectiveness of fibrin glue after elective hepatic resection of benign and malignant lesions in 77 patients. They showed that fibrin glue achieved complete biliostasis.[26] In another study, the common bile duct was resected and an incomplete choledochocholedochostomy was performed over a T tube in 18 pigs. An absorbable polyethylene glycol/collagen biopolymer sealant (CT3; Cohesion Technologies, Inc., Palo Alto, CA) effectively prevented leaks from incomplete biliary reconstructions following these procedures.[40] Nowadays, the bile duct is commonly repaired without using a T tube, with a good postoperative outcome.[41] Using sealants may be advantageous for primary common bile duct repair. Another study demonstrated that fibrin glue significantly decreased the surgically associated segregation of blood or bile from the resection area for 24 h after surgery in 25 patients.[42] A randomized trial showed that classical fibrinogen/thrombin glue and collagen powder were equally effective after elective liver resections in 62 patients and both methods showed similar hemostatic effects.[43] Some studies have suggested that a fibrin sealant may reduce the incidence of postoperative bile leakage[6,42] and reduce the concentration of bilirubin in drain fluid on the first postoperative day.[28] Taken together, the above-mentioned studies have demonstrated the effectiveness of different sealants in improving the postoperative outcome after hepatobiliary operations.

Precise surgery and intraoperative detection and suturing of bile leakages are the best way to reduce and prevent bile leaks and the use of sealants should not be recommended as a primary choice for all patients. Recently, several new methods, such as fluorescence imaging, have been developed to detect and prevent bile leakage after hepatectomy.[44] Indocyanine green fluorescence imaging provides a safe and reliable contrast for detecting intra-hepatic bile leakage following liver resection. To optimize the surgical procedure and reduce the risk of posthepatectomy bile leakage, sealants have been used worldwide. However, there is still no strong clinical evidence that fibrin sealants reduce the incidence of bile leakage after liver resection. The majority of published studies evaluated intraoperative hemostatic efficacy and did not investigate postoperative bile leakage.[28,30,31,45–48] Boonstra et al showed that bile has profibrinolytic effects and anticoagulant properties *in vitro*. They demonstrated that fibrinolytic proteins in bile accelerate the lysis of plasma clots and break down fibrin sealants.[49] In a recent multicenter randomized trial including 310 patients, the prophylactic application of a fibrin sealant to the resection surface of the remnant liver did not reduce the incidence or severity of postoperative bile leakage.[28] Others have reported no significant improvement after application of sealants compared with no sealants. Dimo et al (1989) reported that fibrin sealants had no effect on postoperative peritoneal drainage after elective cholecystectomy in 80 patients.[50] A retrospective study of 616 consecutive hepatectomy patients between 1989 and 1998 showed that the postoperative methylene blue test reduced biliary leakage, whereas a post-resection cholangiography or application of fibrin glue had no effect.[9] Although these studies indicated that fibrin sealants do not significantly improve postoperative bile leakage, they did not reveal any complications or disadvantages of using sealants.

There were some limitations to this study. First, to assess the biliostatic potential of different sealants, we used a perforated gallbladder as a model of biliary system injury. Another limitation of our study was that, to investigate the association of pressure changes and bile leakage, perforations in the control group were not treated with any standard clinical interventions, therefore the control group did not resemble routine clinical practice. Based on our findings, we concluded that modern sealants significantly improve biliostatic properties following liver surgery. In addition, we demonstrated that different sealant materials have different biliostatic effects. Further experimental studies with long-term follow-ups are needed to evaluate the adherence and resistance of different sealants as well as their histopathologic interaction with the resection surface and their effect on posthepatectomy liver regeneration. Therefore, the advantages and disadvantages of using sealants should be carefully considered in each individual clinical setting. The effectiveness of sealants should be evaluated in clinical studies as an adjunct to current procedures. Future prospective randomized-controlled trials can establish the indications and criteria for using sealants in the clinical setting.

Conflicts of interest statement

The authors declare that there is no conflict of interest.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Appendix A. Supplementary data

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