Prevention of Biliary Leakage after Partial Liver Resection Using Topical Hemostatic Agents

Deha Erdogan Olivier R.C. Busch Dirk J. Gouma Thomas M. van Gulik

Department of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

Key Words

Biliary leakage, incidence and risk factors • Biliary leakage, prevention • Partial liver resection • Topical hemostatic agents • Topical hemostatic agents, biliostatic efficacy

Abstract

Liver resection is widely accepted as the only potentially curative treatment in malignant or benign hepatobiliary lesions. Although not frequent, biliary leakage is a postoperative complication which may have considerable consequences. The field of topical hemostatic agents is rapidly developing, with various products currently available. This article reviews the risk factors associated with biliary leakage and the methods used for testing or prevention of biliary leakage. A literature search was performed using key words related to experimental and clinical studies dealing with biliary leakage. Experimental studies assessed the potential biliostatic effect of different topical hemostatic agents after bile duct reconstruction. Clinical series show biliary leakage rates up to 12%. There is no evidence that flushing of the bile duct system after resection reduces the incidence of biliary leakage. Further controlled studies are needed to clarify the preventive effect of topical hemostatic agents on biliary leakage after liver resection.

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Introduction

Liver resection is widely accepted as the only potentially curative treatment in malignant or benign hepatobiliary lesions. In recent years, morbidity and mortality rates have markedly decreased because of the refinements in surgical techniques, improved selection criteria and advances in postoperative care [1, 2]. The most important complications after liver resection are bleeding, intra-abdominal infection and liver failure due to insufficient remnant liver function. Although not very frequent, biliary leakage remains a problem with a reported incidence ranging from 3.6 up to 12% [1, 3, 4]. The techniques used during liver resection for closure of bile ducts on the resection surface are still insufficient to prevent this complication completely. Postoperative biliary leakage may result in abdominal sepsis and even postoperative mortality. Currently, various topical hemostatic agents such as fibrinogen-coated collagen patches as well as fibrin glues have been developed for surgical tissue management [5, 6]. Although the main goal of using these agents is hemostasis of the resection surface, there is an increasing interest in the biliostatic effect of these topical hemostatic agents [7].

The aim of this paper is to review the literature on the incidence and the risk factors of biliary leakage after par-

tial liver resection. Secondly, several methods used for detection of biliary leakage during liver resection are described. Finally, the biliostatic potential of topical hemostatic agents used after liver resection is assessed.

Incidence and Risk Factors of Biliary Leakage

Despite advances in surgical techniques, a wide range of the incidence of biliary leakage is still reported in literature. Reasons for this are the lack of a worldwide uniform definition and the different patient populations analyzed in the various reports. Also, in certain instances, a minor biliary leak will resolve without being noticed during hospital stay. Therefore, it is difficult to make comparisons concerning this complication in the published series on liver resections.

In our center, a recent analysis of 286 consecutive liver resections performed during a period of 13 years showed postoperative biliary leakage in 10.1% of patients. Especially patients with bile duct tumors, who had undergone liver resection with concomitant bile duct resection and biliary-digestive reconstruction, had a significantly higher biliary leakage rate of approximately 28.9% (15/52 patients) [8], as was comparable with other reports [9]. Since these patients had undergone a biliary-enteric anastomosis, they were obviously more prone to develop this complication [10]. In the remaining 234 patients who had undergone liver resection without biliary reconstruction, biliary leakage occurred in only 6.8% of patients (16/234). In our series, the main indication for partial liver resection was colorectal tumor metastases showing biliary leakage in 9.9% (12/121) of patients. Patients resected for benign lesions showed biliary leakage in 4.3% of patients (3/70).

To our knowledge, there are only few large series investigating the incidence of biliary leakage after partial liver resection without concomitant hepaticojejunostomy. A recent analysis by Capussotti et al. [4] showed biliary leakage in 3.6% of patients, which is the lowest reported rate in the literature. In the study of Yamashita et al. [3], biliary leakage had occurred in 4% of patients. Nagano et al. [11] reported biliary leakage in 5.4%. Other studies showed biliary leakage in 5.8% [12], 7.2% [13] and 8.1% [14] of patients. The highest rate was reported by Reed et al. [1] who analyzed 74 patients, of whom 9 (12%) showed biliary leakage. Also in this study, however, biliary leakages after resection for the remaining indications were not shown (table 1).

Table 1. Overview of clinical studies focusing on biliary leakage after partial liver resection

Group (first author)	Patients included	Bile leakage	Main indication for resection
Capussotti [4]	610	22 (3.6%)	CRM (256; not shown) HCC (214; not shown)
Yamashita [3]	781	31 (4%)	HCC (604; 4%)
Nagano [11]	313	17 (5.4%)	Metastases (187; 4.3%) HCC (126; 7.1%)
Lee [12]	605	35 (5.8)	HCC
Tanaka [20]	363	26 (7.2%)	HCC (316; 7.3%)
Lo [14]	347	28 (8.1%)	HCC (211; not shown)
Reed [1]	74	9 (12%)	Metastases (not shown)

CRM = Colorectal tumor metastases; HCC = hepatocellular carcinoma.

The direct consequences of postoperative biliary leakage may be considerable [15]. Especially patients with persisting biliary leakage are more susceptible to develop intra-abdominal sepsis and show prolonged hospital stay. In certain cases, intra-abdominal sepsis may lead to postoperative liver failure and even to death [16], as was shown by the study of Yamashita et al. [3]. Patients with biliary leakage were significantly at increased risk for hospital mortality compared to those without (6.5 vs. 1.2%, $p = 0.007$). Another study with similar results showed that patients with biliary complications had a significantly higher mortality compared to those without (39.3 vs. 6.0%, respectively, $p < 0.0001$). Therefore, in case of suspicion of biliary leakage, early detection using imaging studies and adequate, subsequent treatment is mandatory to prevent mortality [13, 17].

Several mechanisms are thought to be responsible for biliary leakage after liver resection, such as unrecognized bile ducts at the resection surface which continue to leak [18], damaged bile ducts at the liver hilum during the liver transection procedure, and spasm of the sphincter of Oddi with consecutive increase in intrabiliary pressure [19]. It has been reported that biliary leakage is more common after extended hemihepatectomies [14]. The leakage usually originates from transected intrahepatic bile ducts in the resection surface, whereas leakage from extrahepatic bile ducts is the result of a direct injury or leakage from the closed stump(s) of the right or left hepatic ducts. Although the technique of liver resection has seen remarkable refinements in the past decade, the rate of biliary leakage still has remained constant without any substantial decrease [14, 15].

Therefore, knowledge of specific risk factors is thought to be useful to identify patients at risk for biliary leakage after liver resection. However, to our knowledge, few studies have focused on associated factors of biliary leakage to reduce this complication. Yamashita et al. [3] identified high-risk procedure, intraoperative blood loss, and surgical time using univariate analysis. Logistic regression identified only high-risk procedures to be significant. In this study, high-risk procedures consisted of procedures in which the cut surface exposed the major glissonian sheath and included the liver hilum, such as in anterior segmentectomy, central bisegmentectomy, and total caudate lobe resection. The correlation between prolonged surgical time and biliary complications is not quite evident, but is thought to be associated with technically difficult and complicated surgical procedures.

Capussotti et al. [4] identified that among all types of major liver resection, only left hepatectomy with concomitant resection of segment 1 was a significant high-risk procedure for biliary leakage ($p < 0.001$). The risk of biliary leakage did not show any increase when a classic left liver resection, without segment 1, was performed. The presence of liver cirrhosis was associated with a significantly lower biliary leakage (2/167 [1.2%] vs. 20/443 [4.5%], $p = 0.05$). Probably, this could be explained by the less extensive procedures performed in patients with an underlying parenchymal liver disease in order to prevent the chance of postoperative liver failure. However, multivariate analysis failed to show that cirrhosis had any influence. The only independent risk factors for biliary leakage were resection of a peripheral cholangiocarcinoma ($RR = 5.47$, $p = 0.02$) and segment 4 resections ($RR = 3.10$, $p = 0.02$). An interesting co-finding was that fibrin glue applied on the resection surface to improve hemostasis showed to be the only independent protective factor ($RR = 0.38$, $p = 0.046$).

According to the results of Tanaka et al. [20], patients with cirrhosis had a lower incidence of biliary leakage, but the difference was not statistically significant (4.5 vs. 8.7%, $p = 0.20$). Nagano et al. [11] detected advanced age, large incisional surface areas, and high-risk operations (procedures associated with exposure of the major glissonian sheath around the liver hilus) significant on univariate analysis. In this study, high-risk procedures included a central hepatectomy (resection of segments 4, 5, and 8), right anterior sectionectomy (segments 5 through 8), caudate lobectomy, or resections including segments 4, 5, and 8 [3, 11]. However, no multivariate analysis was performed in this study. Lee et al. [12] concluded in their study that for patients with hepatocellular carcinoma,

preoperative chemoembolization ($OR = 3.274$, $p = 0.005$) and centrally located tumors ($OR = 2.927$, $p = 0.003$) were independent risk factors. In the study of Lo et al. [14], stepwise logistic regression analysis identified increasing age, higher preoperative white blood cell count, left-sided hemihepatectomy, and prolonged operation time as the independent factors for biliary leakage. For the performance of left-sided procedures, the authors gave an anatomical explanation that bile ducts from the caudate lobe and, not infrequently, the duct from the right posterior segment drains into the left main duct. Therefore, they postulated that the risk of damaging is higher when the left hepatic duct is divided close to the liver hilum. This is also reflected by the results of Capussotti et al. [4]. Therefore, Lo et al. [14] suggested using cholangiography before partial liver resection to identify possible anomalies of the biliary tract. However, a recent study on biliary complications after living donor liver transplantation showed biliary leakage in 2.5% (7/276) of patients, and all of them occurred after right-sided liver resection [21]. In our analysis, the majority of biliary leakages also occurred in patients after right hepatectomy (9/16 [56.3%]), followed by extended right hemihepatectomy (4/16 [26.7%]).

Methods for Prevention and Detection of Biliary Leakage

Although several studies have focused on different methods for testing of biliary leakage after liver resection, its usefulness is still debated. The methods described in the literature include a direct test with injection of isotonic sodium chloride or a dye [14, 15, 22], injection of air to assess bile duct patency under ultrasound guidance [23] and cholangiography before or during the surgical procedure [24]. The aim of these tests used during the surgical procedure is to visualize possible insufficiently closed bile ducts at the resection surface of the remnant liver by irrigating the bile ducts under elevated intrabiliary pressure. Various agents can be used for these tests including isotonic sodium chloride or a dye (indocyanine green or methylene blue). Ijichi et al. [19] published the results of a randomized trial to assess the use of a direct test for testing biliary leakage. For this test, a balloon catheter was inserted through the cystic duct after cholecystectomy and inflated. Thereafter, isotonic sodium chloride was injected through the cystic duct filling the intrahepatic biliary system. Subsequently, the bile ducts on the resection surface showing leakage were closed

with interrupted sutures. In the group of patients in which the test was used, a total of 21 patients (41%) showed biliary leakage and were suture closed. Nevertheless, there was no significant difference in postoperative biliary leakage rate between the two groups (6 vs. 4%, $p = 0.99$). The authors concluded that methods for testing of biliary leakage should not be used routinely during a partial liver resection, and is only indicated in case of a high suspicion on leakage or damaged bile ducts. However, in both patient groups, fibrin sealants were used and therefore may have prevented differences in the biliary leakage rate in the group without testing. These topical hemostatic agents may have the ability to seal surgically non-suturable bile duct lesions in the surface of the remnant liver, thereby preventing biliary leakage.

The method used in the study of Yamashita et al. [3] for testing biliary leakage consisted of the injection of diluted indocyanine green (green dye) through a cholangiography catheter fixed in the cystic duct. Using this method, the common bile duct was manually clamped by the surgeon. Thereafter, small biliary leakage sites recognized on the resection surface were suture closed. No biliary leakage was seen after 102 consecutive liver resections in whom the biliary leakage test was performed compared to 679 liver resections without a test showing 31 cases of biliary leakage (0 vs. 4.6%, $p = 0.03$). However, it must be remarked that the patients were not randomized, and secondly, the group of patients were operated in different time periods which may have biased the results.

Lam et al. [15] used methylene blue for testing of biliary leakage in 304 (49.4%) patients. Of the patients who had undergone a test, 60 patients showed a positive test and 244 patients were negative. The total leakage rate in the patients with the test was 3.6% compared to 7.4% (23 patients) in the 312 patients without a test ($p < 0.05$). However, the patients in this study were not randomized and significantly more patients had a test during the second 5-year period compared to the first period (238 vs. 66, $p < 0.0001$).

Another method proposed to test biliary leakage is direct cholangiography before undertaking the liver resection to detect whether anomalies of the biliary tree are present [24]. It has also been suggested to use this method after the resection to detect a possible leaking bile duct. However, studies have failed to show the effectiveness of cholangiography in decreasing biliary leakage [24]. It should be noted that a negative result of direct cholangiography or a test using dye or isotonic sodium chloride cannot exclude the possibility of biliary leakage. Espe-

cially in case of a separated bile duct without communication with the main biliary tree, continuous leakage may be present without being detected by using the methods for testing biliary leakage.

Only one study has investigated the use of omentoplasty in sealing the resection surface completely after partial liver resection. However, no significant differences were seen in the rate of abdominal complications (including biliary leakage) in the group with omentoplasty compared to the group without [18]. The authors concluded that omentoplasty should not be used routinely to prevent biliary leakage from the resection surface.

Biliostatic Efficacy of Topical Hemostatic Agents

Although topical hemostatic agents are applied on the resection surface of the remnant liver for hemostasis, the usefulness in preventing biliary leakage by complete sealing of the resection surface still remains unclear and needs to be assessed. Until now, only limited studies have been performed to assess the potential biliostatic effect of these different topical hemostatics.

The first experimental study was performed by Kram et al. [25] to assess whether common bile duct anastomosis or defects could be sealed by using fibrin glue. Ten mongrel dogs had undergone a primary end-to-end common bile duct anastomosis after sharp transection and the anastomoses were covered with 1–2 ml of self-made multicomponent fibrin glue. Only 1 dog showed leakage of the anastomosis 1 week after the procedure, explained by the authors to be the result of inadequate attachment of the CBD segments. Only 7 dogs (70%) underwent cholangiography at postoperative intervals varying from 1 to 6 months to assess the anastomosis. One dog showed a slight narrowing of the CBD anastomosis. However, the early biliary leakage rate could not be evaluated in this setting. In this study, no control group was used for comparison.

The study by Couto et al. [26] was designed to assess 'objectively and quantitatively' the efficacy of autologous fibrin sealant in the sealing of the CBD. The disadvantage of the method to acquire the fibrin sealant was the time required to yield the required fibrinogen, which took approximately 3 h. The fibrin sealant formed after combining the fibrinogen concentrate with the reconstituted thrombin was used as an adjunct to suture closure of a standard 1-cm choledochotomy. Sixteen dogs were divided into two groups. The area with the sutured CBD segment was subsequently placed under a pressure of 40 cm.

The initial mean volume of leakage before application of the fibrin sealant was 16 ml/h and was reduced to zero in the study group. Although no statistical test was used, the authors concluded that fibrin sealants may be valuable in biliary tract procedures in patients with traumatic or iatrogenic injuries.

Jones et al. [27] performed a randomized experimental study to assess the technical ability to perform a laparoscopic choledochojunostomy with fibrin sealants. A total of 21 female pigs were divided into three groups. The procedures were undertaken 3 days after ligation of the common bile duct. In the first group with open laparotomy, a side-to-side choledochojunostomy was performed. In the laparoscopic group, only a choledochojunostomy with four stay sutures was done.

In the second laparoscopy group, fibrin sealant was used on the anastomosis. In the group with fibrin sealant, three anastomotic leakages (43%) were seen in the first postoperative week ($p < 0.05$). However, it was not clear from the study description whether circumferential application of the fibrin sealant was achieved and why biliary leakage had not occurred in the remaining laparoscopic group without fibrin sealant. The authors concluded that fibrin sealant reduces the surgical time without having additional value to reduce biliary leakage.

Wise et al. [28] tested absorbable polyethylene glycol/collagen biopolymer sealant in a randomized experimental study. Eighteen pigs underwent transection of the CBD and an incomplete end-to-end choledochocholedochostomy leaving a defect of one-sixth circumferential anteriorly. Thereafter, the sealant was applied around the circumference of the choledochocholedochostomy with an extra application over the defect. The group without sealant showed higher drain output of bile over the first 4 postoperative days compared to the group with sealant ($p < 0.05$). The rate of bile leakage was reduced from 56% (5/9) to 11% (1/9) ($p < 0.05$). The authors concluded that sealant was effective in decreasing bile leakage in an incomplete choledochostomy porcine model.

The above-mentioned experimental studies only investigated the value of different topical agents on the prevention of biliary leakage after bile duct reconstruction in very preliminary settings. Therefore, the differences in the concentrations of these self-made fibrin sealants and the differences in mixture of the components may have been responsible for variations in the results obtained from these experimental studies. Nowadays, the availability of commercial ready-to-use sealants requires new studies to be performed. Also, a clinically relevant, porcine liver resection model is required to analyze the exact

adhesive strength on the resection surface of the remnant liver of these different sealants to assess the biliostatic efficiency by complete sealing.

Noun et al. [29] reported the results of a French multicentered randomized trial on the effectiveness of fibrin sealants after elective liver resection. The mean total fluid drainage during the 3 postoperative days was significantly lower in the group with fibrin glue (respectively 242 ± 249 vs. 505 ± 666 ml). The bilirubin concentration in the drainage fluid was also lower compared to the group without fibrin glue (24 ± 21 vs. 65 ± 47 mmol/l). Nevertheless, the study failed to show a lower biliary leakage rate or abdominal collections in the treatment group, presumably because of the small numbers of included patients. Recently, a study with primary focus on biliary leakage showed a reduction to 5%, probably because of hemostatic sealants on the resection surface [7, 19].

Two clinical studies demonstrated indirectly the biliostatic efficiency of topical hemostatic agents after liver resection. As mentioned before, Ijichi et al. [19] failed to show that methods testing for biliary leakage could be beneficial to prevent this complication. However, it was remarkable that their overall biliary leakage rate was 5% (test group 6% and control group 4%). Although this low rate might be explained by the application of fibrin sealants on the resection surface of the remnant liver in both groups, the conclusion may be drawn that fibrin sealants cannot prevent all leakages from bile ducts on the resection surface with certainty. Hayashibe et al. [30] analyzed 88 patients after liver resection without biliary reconstruction. The first group of 37 patients with fibrin glue on the resection surface showed biliary leakage in 8.1%, and the second group of 51 patients in whom fibrin glue was combined with bioabsorbable polyglycolic acid sheet showed no postoperative biliary leakage at all ($p = 0.003$). The authors concluded that the combination of fibrin glue and bioabsorbable PGA would be efficient to prevent biliary leakage after liver resection. However, Lam et al. [15] failed to show a reduction in biliary leakage by using fibrin glue (7.2 vs. 4.2%).

In our center, injection of the biliary system with saline for the detection of biliary leakage is usually performed after resection of the liver. Thereafter, topical hemostatic agents such as a fibrin glue or fibrinogen-coated collagen patch are used according to the surgeon's preference. Clearly, before recommendations can be made, the precise benefits of application of liquid fibrin sealants or fibrinogen-coated collagen patches on the resection surface should be investigated in large randomized clinical

studies with clear endpoints. It is also important that the definition of biliary leakage should be based on consensus.

In conclusion, the available studies analyzing liver resections use different criteria to define biliary leakage, including the volume of the abdominal drain output, the bilirubin concentration in abdominal drains and extrav-

asation of contrast during cholangiography. There are still no standardized methods to prevent biliary leakage because of the lack of clear evidence that support their use. After having reviewed all the available literature, there is no clear proof of the biliostatic efficacy of topical hemostatic agents used after liver resection on the resection surface.

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