Incidence and management of postoperative bile leaks: A prospective cohort analysis of 467 liver resections

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Background: Bile leaks from the parenchymal transection margin are a major cause of morbidity following major liver resections. The aim of this study was to benchmark the incidence and identify the risk factors for postoperative bile leakage after hepatic resection.
Patients and methods: A prospective database of 467 consecutive liver resections performed by the University of Cape Town HPB surgical unit between January 1990 and January 2016 was analysed. The relationship of demographic, clinical and perioperative factors to the development of bile leakage was determined. Bile leak and postoperative complications severity were graded using the International Study Group of Liver Surgery and Accordion classifications.
Results: Overall morbidity was 24% (n = 112), with bile leaks occurring in 25 (5.4%) patients. Significantly more bile leaks occurred in patients who had major resections (≥ 3 segments) and longer total operative times ($p < 0.05$). There were 5 Grade A bile leaks which stopped spontaneously. Seventeen Grade B leaks required a combination of percutaneous drainage (n = 15), endoscopic biliary stenting (n = 8) and **percutaneous transhepatic biliary drainage** (n = 3). All 3 Grade C leaks required laparotomy for definitive drainage. Median hospital stay in the 442 patients without a bile leak was 8 days (IQR 1–98) compared with 12 days (IQR 6–30) for the 25 with bile leaks ($p < 0.05$) with no mortality. Major resections (≥ 3 segments) and total operative time (> 180mins) were significantly associated with bile leaks.
Conclusion: The incidence of bile leakage was 5.4% and occurred after major liver resections with longer operative times and resulted in significantly extended hospitalisation. Most were effectively treated nonoperatively by percutaneous drainage of the collection **and/or endoscopic or percutaneous biliary drainage** without mortality.
Key words: operation, liver resection, bile leak.

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Introduction

Advances in surgical technique and improved perioperative management have substantially reduced morbidity and mortality following major liver resections (LR).[1,2] In most major centres mortality after complex liver resections has decreased to less than 3% and morbidity to under 30%.[3,4] Despite the decrease in overall complications, postoperative bile leakage (POBL) remains a significant complication and is a major contributor to morbidity after hepatectomy leading to prolonged hospital stay and the need for further intervention. Persistent or uncontrolled bile leaks may result in abdominal sepsis, liver failure or death.[5] The reported incidence of POBL after LR without biliary reconstruction ranges from 0% to 27.2% and LR with hepaticojejunostomy (HJ) from 3.6% to 50%.[6-9] This wide variation in earlier studies has in part been due to the lack of a uniform definition for bile leakage after liver resection.[10] In order to standardize results, the International Study Group of Liver Surgery (ISGLS) has since proposed a definition and grading system for the severity of bile leakage after hepatobiliary surgery.[6]

The frequency, complexity, type of intervention required and outcome of bile leaks are influenced by the indication and extent of liver resection. The incidence is higher after

central hepatectomy, right anterior sectoral resection, left trisegmentectomy and caudate lobe resections. Leak rates are also higher when LR is combined with resection of the hepatic duct confluence with complex hepaticojejunal anastomoses.[7,8,9] The management of POBL has evolved from obligatory laparotomy to conservative and nonoperative minimally invasive strategies such as percutaneous drainage and endoscopic biliary intervention. Most persistent bile leaks will resolve after minimally invasive intervention and only a minority will ultimately require a repeat laparotomy.[6] The aim of this study was to determine the incidence and identify the risk factors for POBL after LR and establish optimal treatment.

Methods

Study design and data collection

A prospective departmental database of 467 consecutive liver resections performed in the HPB surgical unit at Groote Schuur Hospital and at the Netcare UCT Private Academic Hospital between January 1990 and January 2016 was reviewed. Current guidelines of good clinical practice were followed and data collection and analysis were approved by the departmental, institutional and university research and ethics review boards. Data reviewed included patient demographics, imaging studies, operative data including the extent of surgery, number of liver segments resected, duration and method of inflow occlusion, operative blood loss, the need for transfusion and postoperative morbidity. Perioperative risk factors related to the development of bile leakage were identified and evaluated. Postoperative data including blood transfusion requirements, general and liver specific complications including bile leaks, ICU time as well as hospital stay were included. Clinical presentation of the bile leak, the need for intervention (minimally invasive or open) and the outcome were all evaluated. Intervention was either by ultrasound-guided percutaneous catheter drainage, endoscopic retrograde cholangiopancreatogram (ERCP), percutaneous transhepatic cholangiogram (PTC) or relaparotomy.

Technique of Liver Resection

A standardised operative technique was used, details of which have been described previously.[11-14] Patients were explored through a bilateral subcostal incision with a vertical extension to the xiphoid cartilage as required. Intraoperative ultrasound was performed to define the tumor relationships to major intrahepatic vessels. After full mobilisation, parenchymal transection was performed using a Cavitron Ultrasonic Surgical Aspirator (CUSA). Intermittent total or selective hepatic inflow occlusion for 20 minutes, alternating with 10 minutes of restored inflow was used depending on the extent of blood loss during parenchymal transection. A Roux-en-Y hepaticojejunostomy reconstruction was used when an associated bile duct resection was performed. Multiple intrahepatic bile ducts at the resection margin, when present, were sutured together to create either one or two anastomotic orifices. Haemostasis of the transected liver surface was achieved using 5/0 absorbable monofilament sutures. The parenchymal resection surface was visually assessed for bile leakage by using a white abdominal swab applied to the cut surface for 3 minutes. Any obvious leaks were sutured and the process repeated until no bile leakage was evident. The cut surface was treated with argon plasma coagulation and sealed with Tisseal® spray. The resection margin was routinely drained using closed silastic suction drains.

Definitions

A major hepatectomy was defined as resection of three or more Couinaud liver segments and an extended hepatectomy as resection of five or more Couinaud segments.[15] The Accordion Severity Grading Score (ASGS) was used to score surgical outcomes.[16] Grade I and II complications were defined as minor and grades III, IV, and V were defined as major complications. Postoperative mortality was defined as any death within 30 days after operation. A bile leak was defined as a bilirubin concentration in the drain fluid at least three times the serum bilirubin concentration on or after postoperative day 3 or if a radiologic or operative intervention for a bile collection or bile peritonitis was required.[6] The severity of bile leaks was graded as A, B, or C according to the ISGLS classification.[6] Failure of conservative management was defined as the need for interventional procedures due to complications or because of persistent large volume bile drainage.

Management of bile leakage

Abdominal drains were removed when the drain fluid volume was less than 30 ml/24 hours and was serous with a bilirubin level less than three times the serum total bilirubin level, as defined by the ISGLS. All postoperative bile leaks were initially treated conservatively. Ultrasound and computed tomography were used to detect intra-abdominal or subphrenic fluid collections, if the bile drainage volume did not decrease or there were signs of infection. Significant fluid collections were drained by ultrasound-guided percutaneous catheters. ERC was performed for persistent bile drainage to obtain a cholangiogram to demonstrate the biliary anatomy and the presence and site of a leak.[17] An endoscopic sphincterotomy, sphincterotomy and stenting or stenting alone using 10-Fr plastic stents were performed according to the endoscopic biliary findings. Repeat ERC was performed 2 weeks after resolution of the biliary leak to confirm healing of the biliary fistula and to remove the plastic stent.[18] **Percutaneous transhepatic biliary drainage (PTBD)** was used to decompress the hepatic ducts if a leak was present after hepaticojejunostomy. Reoperation was considered only in patients with biliary peritonitis or sepsis and failure of percutaneous intervention.

Data analysis

The data were analysed using Stata version 11 (StataCorp. 2009. Stata: Release 11. Statistical Software. College Station, TX: StataCorp LP). For bivariate analysis the Pearson chi-square or Kruskal-Wallis tests were used for categorical

variables, and the non-parametric Wilcoxon rank-sum test for numerical variables. All statistical tests were two-tailed and a p-value < 0.05 was considered statistically significant.

Results

Demographic and clinical parameters of patients with and without bile leakage are summarised in Table 1. Colorectal cancer liver metastases were the most common indication for LR. Overall 112 (24%) of the 457 patients developed postoperative complications of which bile leaks occurred in 25 (5.4%) (16 women, 9 men, median age 50 years, range 18–67). Twenty-one patients (84%) had 3 or more segments resected and four had 2 segments resected. During resection eight patients did not require vascular control, 16 had portal vein and hepatic artery clamping and 2 had a hilar dissection with ipsilateral portal vein and hepatic artery division. In these 25 patients, total median ischaemic time was 35 minutes (0–80 minutes) with a longest uninterrupted median ischaemic time of 25 minutes (range 14–54 minutes). Six patients were clamped once and the remaining 10 between 2 and 5 times. The median estimated blood loss (EBL) during surgery was 800 ml (range 250–3 000 ml). Of the 10 patients who had an EBL > 1 000 ml, 7 were transfused intraoperatively (range 1 250–3 000 ml) and one patient received a postoperative transfusion. In one patient in whom haemostasis was not achieved during surgery, the liver was packed with subsequent removal of packs 48 hours later. Median total operative time was 294 minutes (180–528 minutes). The median postoperative ICU time for patients with a bile leak was 3.4 (0–8 days). Median hospital stay in the 442 patients without a bile leak was 8 days (range 5–98) compared with 12 days (range 6–30) for those with bile leaks ($p < 0.05$).

The severity of the bile leaks were grades A = 5, B = 17 and C = 3 according to the ISGLS classification. Significantly more bile leaks occurred in patients who had major resections (≥ 3 segments) and total operative time of more than 180 minutes ($p < 0.05$) (Table 1). Bile drainage stopped spontaneously (median 22 days, range 16–32 days) in five patients. In 4 patients with persistent bile drainage through the intraoperatively placed surgical drain, an ERCP with endoscopic sphincterotomy and 10Fr plastic biliary stent placement was performed with resolution of the bile leak in all four. In 10 patients ultrasound-guided percutaneous drainage was used for loculated bile collections with resolution of the bile leak in six patients. In four with persistent bile drainage, endoscopic biliary stenting was necessary with resolution in all. Some patients required more than one type of intervention when initial intervention failed to resolve the leak. In three patients with multiloculated infected subphrenic bile collections, a second laparotomy was necessary for effective drainage, one patient requiring a third laparotomy for recurrent sepsis. Three patients who had a LR and bile duct resection for cholangiocarcinoma had a bile leak at the site of the hepaticojejunostomy. All three had ultrasound guided aspiration and drain placement and as these were not accessible for endoscopic stent placement, temporary internal-external biliary catheters were placed via percutaneous transhepatic access until resolution. One patient required a thoracotomy for an infected bile collection which had not resolved after tube drainage. No in-hospital mortality occurred in patients with POBL.

Eight of the 25 patients also developed other surgical complications which included wound sepsis (n = 4; ASGS grade 2) and an intra-abdominal collection in one patient (ASGS grade 3) which was drained percutaneously. Non-surgical complications included two ASGS grade 2 events (pneumonia n = 1, ARDS n = 1). One patient developed acute pancreatitis (ASGS grade 2) which was treated conservatively.

Discussion

Despite decreasing mortality and a decline in the overall complication rates of LR in recent years, there has been no significant change in the incidence of POBL. This complication remains a substantial cause of morbidity after LR and may result in prolonged hospitalization with the need for additional imaging and intervention. Furthermore, when major bile leaks are associated with intra-abdominal sepsis, mortality may be as high as 40%. This study focused on the incidence, risk factors and management of POBL after LR in patients with and without associated bile duct reconstruction. Previous studies report an incidence of POBL after LR ranging from 3.6 to 33%.[19-25] The POBL rate in our study of 5.4% was consistent with data in previous reports. Few studies have published results of bile leakage after liver resection with biliary reconstruction. Recent reports of a 21% incidence of POBL in patients who underwent LR with biliary reconstruction compared to 4.6% in patients without a biliary anastomosis[26] are similar to our data.

In our study significantly more bile leaks occurred in patients who had major resections (≥ 3 segments) and longer total operative times ($p < 0.05$). Other authors have reported that risk factors for bile leakage after LR are tumour size, preoperative chemoembolization, repeat hepatectomy, extended right hepatectomy, left hepatectomy including segment 1, duration of vascular occlusion, long operative time (> 300 min), intraoperative blood loss > 775 ml, and intraoperatively treated bile leakage.[19-31] In a subsequent meta-analysis of 18 retrospective studies, 12 factors were found to be significantly associated with the increased rate of POBL. These included previous liver or biliary surgery, anatomic resection, major hepatectomy, right anterior sectionectomy, left trisectionectomy, central bisectionectomy, blood transfusion, long operative time, bile duct reconstruction and involvement of segments 1, 2 and 5.[5]

Several intraoperative strategies have been used in an attempt to prevent POBL but none have gained wide acceptance. POBL-prevention strategies are broadly divided into (i) methods of intraoperative bile leak detection, (ii) prevention by topical sealing or suturing and (iii) biliary drainage to reduce ductal pressure. Methods of intraoperative detection of potential leaks at the transection margin include cholangiography, trans-cystic duct injection of saline, dye (methylene blue, indigocarmine) or air and indocyanine green (ICG) fluorescent imaging.[32-35] The disadvantage of transcystic dye injection is that the dye stains surrounding parenchyma which makes it difficult to pinpoint leaks after the

Table 1. Bivariate Analysis of factors associated with postoperative bile leakage

	Patients who developed a bile leak	Patients who did not develop a bile leak	p-value
	25	445	-
Gender			
Male	16 (64%)	205 (46.4%)	
Female	9 (36%)	237 (53.6%)	0.1009
Age			
< 65 years	20 (80%)	330 (74.7%)	
≥ 65 years	5 (20%)	112 (25.3%)	0.6423
Diagnosis			
CRLM	12 (48%)	214 (48.1%)	1.0000
Intrahepatic stones	4 (16%)	28 (6.3%)	0.0826
HCC	2 (8%)	38 (8.6%)	1.0000
Carcinoid	1 (4%)	15 (3.4%)	0.5998
Biliary cystadenoma	1 (4%)	15 (3.4%)	0.5998
Cholangiocarcinoma	3 (12%)	31 (7%)	0.4142
GIST	1 (4%)	3 (0.7%)	0.1981
FNH	0	19 (4.3%)	0.6144
Haemangioma	0	22 (5%)	0.6217
Sclerosing cholangitis	1 (4%)	0	0.0535
Right lobe resection			
4 segments	9 (36%)	124 (28%)	0.3724
5 segments	3 (12%)	32 (7.2%)	0.4212
Left lobe resection			
2 segments	3 (12%)	91 (20.6%)	0.4417
>2 segments	4 (16%)	46 (10.4%)	0.3280
No of segments resected			
1	0	49 (11.1%)	0.0944
2	4 (16%)	148 (33.5%)	0.0804
3	4 (16%)	41 (9.3%)	0.2863
4	14 (56%)	157 (35.5%)	0.0532
5	3 (12%)	47 (10.6%)	0.7417
3 or more segments	21	254	***0.0108***
Hepaticojejunostomy	3 (12%)	26 (5.9%)	0.1968
Duration of operation			
≥ 180min	25 (100%)	346 (78.3%)	***0.0041***
Blood loss			
< 1000ml	15 (60%)	321 (72.6%)	
> 1000ml	10 (40%)	121 (27.4%)	0.1757
Pringle			
< 60min	9 (36%)	165 (37.3%)	1.0000
≥42	7 (28%)	84 (19%)	0.2976
Hospital stay	6–30 (med 12)	1–98 (med 8)	
Postoperative hospital mortality	0	16 (3.6%)	1.000
Other complications per patient	7 (28%)	87 (19.9%)	0.3094

first injection. In a non-randomised study using intraoperative transcystic saline injection, no bile leaks occurred in 102 consecutive liver resections, compared to leak rates of 4.5% in 679 hepatectomies with no leak test performed.[24] Others have found that the saline injection test is fallible because the clear appearance of saline misses small leaks. A newly described technique involving transcystic injection of ICG, followed by fluorescent imaging had a 0% incidence of POBL, compared to 10% in a control group ($p = 0.019$).[35] Data from MD Anderson showed significantly fewer postoperative bile leaks after using an "air leak test" (1.9% vs 10.8%; $p = 0.008$).[36] Small leaks not identified by a leak test using saline could be detected using this technique. In a small number single institution study, Li and colleagues reported that intraductal injection of a 5% fat emulsion, "the white test," to detect bile leakage resulted in a 5.3% POBL in the experimental group compared with 22.9% in the control group ($p < 0.01$). In a systematic review and meta-analysis of bile leakage tests in liver resection, which included eight studies involving 1253 patients, the bile leakage test group had a significant reduction in POBL compared to the non-bile leakage group (RR = 0.39, 95% CI: 0.23 0.67; I (2) = 3%) and that fat emulsion was the solution of choice for the test.[32]

Topical haemostatic sealants, including fibrin glue and polyglycolic acid (PGA) and collagen sheets coated with a fibrinogen and thrombin layer (TachoSil®) applied to the resection margin have been widely used, but their value in reducing bile leakage is controversial. Likewise, there are publications reporting the use of fibrin glues and omental wrapping, but no large randomised or multi-institutional studies exist, and there is no clear consensus on the usefulness of these methods. A prospective, randomised controlled study showed no difference in bile leaks in patients who underwent liver resection with and without application of fibrin sealant.[37] Transcystic duct tube drainage after hepatectomy has been reported to be useful for decreasing postoperative bile leakage. While Hotta[38] observed bile leakage in 3.6% of patients with transcystic duct tube drainage versus 26.3% without drainage, Nanashima[39] found that the POBL rate was no different between the two groups (7.9 vs 8.4%). Further prospective and randomised studies are necessary to clarify the usefulness of transcystic duct tube drainage.

No liver resection technique is immune to POBL and the clamp-crushing technique, stapling, CUSA, radiofrequency dissecting sealer, harmonic scalpel and vessel sealing are all associated with a potential bile leak risk. A meta-analysis demonstrated a decreased risk of POBL using a vessel-sealing system, compared to crush-clamping, CUSA, and radiofrequency dissecting sealer, but randomised controlled trials are needed to fully assess the impact of these transection techniques on POBL.[40]

Minimally invasive techniques are preferred for the initial management of complicated POBL. Percutaneous abdominal drainage for localised bile collections not drained by intraoperatively placed drains is increasingly being used. In patients with persistent bile leaks despite percutaneous drainage endoscopic stenting, using a variety of techniques is successful in 90% of cases and is now the therapeutic procedure of choice.[17,19,41,42] In the current study stent placement was performed in more than half of the patients with 100% resolution of the leak. There is currently no consensus regarding optimal endoscopic intervention, nor are there controlled data to indicate the optimal number, configuration, size and length of endoprostheses required for successful management of POBL. The ideal duration of biliary stenting is not known, and has varied from 3 to 8 weeks in previous reports. We used single 10-Fr plastic stents in preference to smaller 7-Fr stents which carry a risk of early stent occlusion,[18] although a comparative study has found no difference in outcome based on stent diameter. As seen in this study, patients with POBL associated with a HJ can safely be managed by PTBD without the need for relaparotomy.

In conclusion, although there is a spectrum of POBLs, some may be severe and result in substantial morbidity. In this series, the more extensive the liver resection with longer operative times, the greater the risk of POBL, which resulted in significantly longer hospitalisation. In this high risk group particular care should be taken on completion of the resection to identify subtle bile leaks at the liver transection margin. Non-surgical treatment is the preferred treatment of POBL. Percutaneous abdominal drainage and endoscopic stenting was effective in most cases of POBL without a HJ in this study. Percutaneous transhepatic biliary drainage was the treatment of choice for POBL in patients with an associated HJ and is effective and safe.

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