ORIGINAL ARTICLE

Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study

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Abstract

Background: The International Study Group for Liver Surgery (ISGLS) proposed a definition for bile leak after liver surgery. A multicentre international prospective study was designed to evaluate this definition.

Methods: Data collected prospectively from 949 consecutive patients on specific datasheets from 11 international centres were collated centrally.

Results: Bile leak occurred in 69 (7.3%) of patients, with 31 (3.3%), 32 (3.4%) and 6 (0.6%) classified as grade A, B and C, respectively. The grading system of severity correlated with the Dindo complication classification system ($P < 0.001$). Hospital length of stay was increased when bile leak occurred, from a median of 7 to 15 days ($P < 0.001$), as was intensive care stay ($P < 0.001$), and both correlated with increased severity grading of bile leak ($P < 0.001$). 96% of bile leaks occurred in patients with intra-operative drains. Drain placement did not prevent subsequent intervention in the bile leak group with a 5–15 times greater risk of intervention required in this group ($P < 0.001$).

Conclusion: The ISGLS definition of bile leak after liver surgery appears robust and intra-operative drain usage did not prevent the need for subsequent drain placement.

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Introduction

There has been a marked reduction in mortality from liver surgery, but a significant risk in morbidity remains. Many studies have examined the morbidity associated with a liver resection, but there is wide discordance in the incidence of complications. Bile leakage after surgery is one such complication that occurs in 3.6% to 12% of patients undergoing a liver resection without biliary reconstruction[1] and in 0.4% to 8% of patients undergoing a liver resection with biliary reconstruction.[2] This wide variation is in part because of the lack of a standard definition of bile leak after a liver resection.

The International Study Group for Liver Surgery (ISGLS) proposed a standardized definition for bile leak after a hepatic resection in an attempt to include all patients with bile leak and account for variation in pre-operative bilirubin and the variable post use of drains.[3] Because the definition was designed to be inclusive, a grading system of severity was used to stratify the clinical relevance of the leak. The definition is outlined in Table 1. This definition has not yet been evaluated in a prospective manner across multiple centres.

The aim of this study was to evaluate prospectively the ISGLS definition for bile leak after a liver resection in a multicentre and multinational cohort of patients undergoing a liver resection for all indications, with varying hepatic parenchyma quality and varying practices regarding drain usage. To evaluate the performance of the severity grading system of the ISGLS definition of bile leak, its relationship with a general classification of complication severity was explored.

Table 1 International Study Group for Liver Surgery (ISGLS) definition for biliary leak

Definition	Bile leakage is defined as fluid with an elevated bilirubin level in the abdominal drain or intra-abdominal fluid on or after post-operative day three or the need for radiological intervention (i.e. interventional drainage) owing to biliary collections or re-laparotomy due to biliary peritonitis. The elevated bilirubin level in the drain or intraabdominal fluid is defined as a bilirubin concentration at least three times higher than the serum bilirubin level measured at the same time.
Grade	A. Bile leakage requiring no or little change in patients' clinical management
	B. Bile leakage requiring a change in patients clinical management (e.g. additional diagnostic or interventional procedures) but manageable without a re-laparotomy. OR: a Grade A bile leakage lasting for > 1 week
	C. Bile leakage requiring re-laparotomy

Methods

Eleven centres from Australia, China, Germany, Japan, Spain, the United Kingdom and the United States of America participated in this study. Delegates from each of these centres met during the International Hepatopancreatobiliary Association 2010 congress in Beaunos Aries and agreed on the contents of a datasheet used to prospectively collect data from patients undergoing a liver resection performed between July 2010 and July 2011. The data sheet was designed to examine the three ISGLS definitions proposed for a post-hepatectomy haemorrhage, liver failure and bile leakage, focusing on the bile leakage definition in this analysis.[3–5] Consecutive liver resections were included. Data sheets were collated centrally and analysed by an independent co-ordinator. There was deliberately no attempt to standardize practices across the different institutions to provide a 'real-world' view of the performance of the ISGLS definition of bile leak. Information on the patient demographics, indication for surgery, extent of surgical resection, the quality of the liver resected, the use of portal vein embolization, the Pringle manoeuver and drains were collected. Subjective assessments, such as the quality of the liver parenchyma, were left to the judgement of experienced liver surgeons performing the procedure. Decisions on the method of liver transection and whether or not a drain was placed and drain type were also left to the operating surgeons. Details on intra- and post-operative blood loss and transfusion, laboratory parameters such as bilirubin in the serum and drains, international normalized ratio (INR), haemoglobin, and length of stay in hospital and intensive care were collected. In-hospital mortality and details of any interventions and radiological investigations were recorded as were the Dindo–Clavien grading of complicatons.[6] For the purposes of the study, patients were not followed beyond the index admission. The ISGLS definitions of bile leak, liver failure and haemorrhage were used and applied at the end of the admission.[3–5]

Statistical analysis

Data were entered in Microsoft Excel, checked and edited before being transferred and analysed in STATA version 13.0 (StataCorp, 2012). Means and standard deviation (SD) were calculated for continuous data. Proportions were presented as percentages of the respective denominator (n). The median and interquartile range (IQR) were also calculated for skewed data. Proportions were initially assessed using a standard chi-square test for association with continuity correction where appropriate. A generalized linear model with binomial family and log link functions was undertaken. Univariate models were first performed variable by variable, without any adjustment. This was done to explore the association between each variable and the risk of bile leak. Multivariate modelling was undertaken by putting all variables considered clinically important or showing statistical significance in the univariate analysis. This was done to adjust for confounding between variables. A backward elimination approach was used in the multivariate model. Briefly, the full model was fitted with all covariates, representing the ideal. The covariate was then removed with the smallest influence on the risk of bile leak and the procedure was repeated. The estimates were expressed as unadjusted relative risk (RR) from the univariate model and adjusted RR from the multivariate model. The RRs were considered statistically significant if their 95% confidence interval (CI) did not include unity. The more the RR deviated from 1, the stronger the association between the exposure variable and the condition being studied. The GLM model was being undertaken using the *glm* procedure in STATA Version 13.0 (StataCorp, 2012).

Results

The patient and treatment variables of the 949 patients included are shown in Table 2. The technique of resection and drain type were not specifically recorded prospectively. A post-analysis survey indicated most centres employed CUSA (Compact Ultrasonic Surgical Aspirator) or similar and a suction drain was the most commonly used drain type. Of the 69 (7.3%) patients recorded as having a bile leak according to the ISGLS definition, 31 (3.3%) were grade A, 32 (3.4%) were grade B and 6 (0.6%) were grade C. The results of the univariate analysis are summarized in Table 3. While bile leak was more commonly associated with liver fibrosis (RR 2.18, $P = 0.01$), only two bile leaks (both grade A) occurred in cirrhotic patients. The intra-operative blood loss was higher in patients with bile leaks (1209 versus 527 ml, $P < 0.001$) and these patients had a higher likelihood of receiving a blood transfusion immediately post-operatively and more than 6 h post-operatively (RR 1.77, $P = 0.059$ and RR 1.99, $P < 0.01$, respectively). The only variables from Table 3 that were significant factors predicting bile leak on multivariate analysis were drain placement and increasing intra-operative blood loss.

The overall in-hospital mortality rate was 1.6% (15 of 949 patients). Five of the 15 patients who died had a bile leak, two of these were grade A, two were grade B and one was grade C. The