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ORIGINAL ARTICLE

Tc-99m-BrIDA hepatobiliary (HIDA) scan has a low sensitivity for detecting biliary complications after orthotopic liver transplantation in patients with hyperbilirubinemia

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Abstract
Background Tc-99m-BrIDA hepatobiliary scans are noninvasive tests for detecting biliary leaks and obstructions. However, there is low sensitivity and specificity in patients with hyperbilirubinemia. Biliary complications (BC) are the Achilles heel of orthotopic liver transplantation (OLT). We questioned whether hyperbilirubinemia in liver transplant recipients rendered HIDA scanning less dependable.
Methods HIDA findings were compared to endoscopic retrograde cholangiopancreatography, laparotomy, and clinical course. Results were categorized as follows: true positive (TP), true negative (TN), false positive (FP), false negative (FN), or nondiagnostic/inconclusive. We searched for variables associated with erroneous or nondiagnostic tests which we defined as all examinations determined to be FP, FN and/or nondiagnostic/inconclusive.
Results Thirty-four patients underwent a HIDA scan. The sensitivity and specificity were 70 and 100%. The sensitivity of HIDA improved to 100% in patients with a total bilirubin (TB) <5 mg/dl. Inconclusive and FN patients had a total bilirubin >5 mg/dl. One FN had a TB <5 mg/dl, but was determined inconclusive due to the roux-en-Y.
Conclusion HIDA scans performed when the total bilirubin was <5 mg/dl had a high sensitivity and specificity for detecting biliary complications after OLT. However, when the total bilirubin exceeded 5 mg/dl, the specificity was still 100% but the numbers of nondiagnostic/inconclusive and FN exams were increased.

Keywords Hepatobiliary scan · HIDA scan · Hyperbilirubinemia · Orthotopic liver transplantation (OLT)

Introduction

Biliary complications (BC) after orthotopic liver transplantation (OLT) are still an area of major concern despite advances in surgical techniques. The incidence ranges between 10 and 30% [1, 2]. They often manifest as hyperbilirubinemia, and are frequently diagnosed with exploratory laparotomy, endoscopic retrograde cholangiopancreatography (ERCP), Doppler ultrasound (US), magnetic resonance cholangiopancreatography (MRCP) or a combination thereof.

HIDA scans are a noninvasive imaging technique for detecting BC. They have a well-defined role in nontransplanted patients with sensitivity and specificity exceeding 90% [3]. However, the test is only reliable when the bilirubin is <5 mg/dl [3]. It is also a well established, noninvasive, reliable, and sensitive modality for detecting biliary leak, stricture, and obstruction in liver transplantation [4–14]. It is unclear whether HIDA scans in the presence of hyperbilirubinemia after liver transplantation are reliable.

We reviewed our experience with HIDA scans performed to rule out biliary pathology within 60 days after transplantation. We sought to determine the threshold level

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of hyperbilirubinemia that rendered HIDA scans unreliable. We believed HIDA would be unreliable in detecting biliary complications after orthotopic liver transplantation when the total bilirubin is more than 5 mg/dl.

Methods

This was a retrospective IRB approved study. A total of 309 OLT were performed from May 2002 to December 2009. Thirty-four of these patients underwent a HIDA scan due to suspected biliary complications. Indications for HIDA scans included rising total bilirubin, abnormal output from the drains or wound, and abdominal pain. Biliary complications in relation to total bilirubin were analyzed. Complications were categorized as biliary leak, obstruction, or stricture, and were confirmed by ERCP, laparotomy findings, or clinical course.

All HIDA scans were read by the same senior nuclear medicine physician. These scans were obtained by anterior dynamic planar imaging for 1 h, followed by static left anterior oblique and right lateral images, with 4 and 24 h delayed images, with a dual-detector large field of view variable angle gamma camera with low-energy high-resolution parallel hole collimators (Siemens e.cam, Hoffman Estates, IL) following intravenous injection of 6 mCi (222 MBq) of Tc-99m Mebrofenin (BRIDA) (Choletec, Bracco, Princeton, NJ). Hepatobiliary scintigrams were analyzed for hepatic parenchymal dysfunction, biliary complications and intra-/extra-peritoneal leaks.

Variables associated with either erroneous or nondiagnostic tests were evaluated. Erroneous or nondiagnostic tests were defined as false positive (FP), false negative (FN), or nondiagnostic/inconclusive. Liver function tests were reported for the day of the HIDA scans. Results from the HIDA scan were compared to ERCP, laparotomy findings, or clinical course and the accuracy of the reported negative and positive findings were verified. Statistical analyses were performed with SPSS for Windows version 10.0 (SPSS Inc, Chicago, IL, USA). Data are expressed as percentage (%), and median (range). Comparisons between independent groups were performed using Mann–Whitney *U* nonparametric test for continuous variables and the Chi-square test for categorical variables. A p value <0.05 was considered as statistically significant.

Results

OLT and donor procurements were completed by the same senior transplant team. Donor information is reported in Table 1. Thirty-three donor livers were acquired through donation after neurologic death (DND), and one was a donation after cardiac death (DCD). The median cold ischemic time (CIT) was 540 min (401–1032), and median warm ischemic time (WIT) was 54 min (18–96). Median donor age was 51 (19–74), and body mass index (BMI) was 25 (18–36). Donor ethnicity included 29 White, 4 African American, and 1 Hispanic. Twenty-one were male.

Table 1 Donor information

Variable	$N = 34$
Type [*n* (%)]	
DCD	1 (2.9)
DND	33 (97.1)
Age (years) [median (range)]	51 (19–74)
Race [*n* (%)]	
White	29 (85.3)
African American	4 (11.8)
Hispanic	1 (2.9)
Gender [*n* (%)]	
Male	21 (61.8)
Female	13 (38.2)
BMI [median (range)]	25 (18–36)
CIT [median (range)]	540 (401–1032)
WIT [median (range)]	54 (18–96)

DCD donation after cardiac death, *DND* donation after neurologic death, *BMI* body mass index, *CIT* cold ischemic time, *WIT* warm ischemic time

Table 2 Demographic characteristics of study subjects

Variable	$N = 34$
Age (years) [median (range)]	56 (31.6–74.4)
Male [*n* (%)]	27 (79)
Ethnicity-White [*n* (%)]	23 (67)
AST [median (range)]	74.5 (7–5806)
ALT [median (range)]	150.5 (9–3572)
INR [median (range)]	1.2 (0.9–8)
Bilirubin	
Total [median (range)]	4.3 (0.6–29.76)
Direct [median (range)]	3.3 (0.2–19.5)
Time OLT to HIDA	
Days [median (range)]	8.5 (3–60)

AST aspartate aminotransferase, *ALT* alanine transaminase, *INR* international normalized ratio, *OLT* orthotopic liver transplantation, *HIDA* hepatobiliary iminodiacetic acid

Thirty-four patients underwent HIDA scans within 60 days after liver transplantation for evaluation of BC. Their demographics are shown in Table 2. The median age was 56 (32–74) years. Twenty-seven were men. Median values for liver enzymes were aspartate aminotransferase (AST) 74.5 (7–5806), alanine aminotransferase (ALT) 150.5 (9–3572), international normalized ratio (INR) 1.2 (0.9–8), TB 4.3 mg/dl (0.6–29.76), and direct bilirubin 3.3 mg/dl (0.2–19.5). Sixteen patients had a TB >5 mg/dl

on the day of the HIDA scan. Scans were obtained from 3 to 60 days after transplant, with a median of 8 days. Surgical technique included 25 end-to-end common bile duct (CBD) anastomoses with no T-tube, 6 end-to-end with T-tube, and 3 Roux-en-Y choledocho-jejunostomies.

HIDA scans were chosen as the initial screening procedure for patients with a roux reconstruction, a fresh anastomosis, nonavailability of gastroenterologic staff or the preference of the surgeon. Outcomes of HIDA diagnosis are reported in Table 3. Twenty-seven patients were correctly diagnosed. Eight were true positive (TP) and 19 were true negative (TN). There were 7 incorrect diagnoses. None were FP, 3 were FN, and 4 were inconclusive/nondiagnostic.

Parameters affecting the diagnostic outcome of HIDA scans were statistically evaluated and are presented in Table 4. There was a statistical difference between the correct and incorrect diagnosis in TB ($p = 0.003$), direct bilirubin ($p = 0.003$), AST ($p = 0.043$), and ethnicity ($p = 0.022$) in recipients, and WIT ($p = 0.010$) in donors. All other parameters including age, gender, ALT, INR, CIT, time from OLT to HIDA, and donor information except WIT were insignificant when comparing correct versus incorrect diagnosis.

HIDA scans gave an incorrect diagnosis in 7 patients. All but one had at TB >5 mg/dl. Table 5 compares the HIDA scan diagnosis with each patient's final diagnosis and TB at the time of the HIDA scan. There were three reports of no leak, yet a leak was observed in the operating room or by ERCP. Four scans reported inconclusive results. Two of these patients were found to have intact anastomoses, and two were observed with no eventful outcome.

TB above and below 5 mg/dl is compared with outcomes in Table 6. In patients with a TB $\leq$ 5 mg/dl, HIDA gave the correct diagnosis in 17 of 18 patients, compared to 10 of 16 patients with a TB >5 mg/dl. The overall sensitivity and specificity of HIDAs were 70 and 100%. The sensitivity and specificity of HIDAs for patients with total bilirubin >5 mg/dl were 62.5 and 100%. However, the sensitivity improved to 100% in patients with total bilirubin $\leq$5 mg/dl. The specificity remained 100%. There was a statistical difference between correct and incorrect HIDA results in patients with a total bilirubin >5 mg/dl and in those <5 mg/dl ($p = 0.029$).

There were 4 mortalities in this cohort. Three expired from sepsis and one from multiple organ system failure (MOF). The patient with MOF had a FN HIDA and a biliary leak was diagnosed at exploratory laparotomy. Two of the three septic patients had TN HIDA scan. One had a TP HIDA for biliary leak which was confirmed by ERCP. The remaining patients in this study were followed clinically with resolution of symptoms.

Table 3 Tc-99m-BrIDA hepatobiliary scan diagnosis

Diagnosis	*n* (%)	TP	TN	FP	FN	Inc
Correct	27 (79.4)	8	19	–	–	–
Incorrect	7 (20.6)	–	–	0	3	4

TP true positive, *TN* true negative, *FN* false negative, *FP* false positive, *Inc* inconclusive

Discussion

Biliary complications after OLT are common with rates reported as high as 30%, and associated mortality reaching 10% [1, 2, 15, 16]. A review of our own database revealed

Table 4 Diagnostic outcome of HIDA scans

Variable	Correct diagnosis ($N = 27$)	Incorrect diagnosis ($N = 7$)	P value
Age (years) [median (range)]	56.6 (32–74)	56 (49–67)	0.654
Male [*n* (%)]	21 (78)	6 (86)	0.550
Ethnicity-White [*n* (%)]	21 (78)	2 (29)	0.022
AST [median (range)]	74 (7–781)	81 (16–5806)	0.043
ALT [median (range)]	157 (9–1121)	108 (29–3572)	0.128
INR [median (range)]	1.2 (0.9–1.7)	1.2 (1.1–8.0)	0.059
Bilirubin			
Total [median (range)]	2.4 (0.6–14.4)	8.1 (1.3–29.8)	0.003
Direct [median (range)]	1.4 (0.2–12.5)	7.0 (0.3–19.5)	0.003
Time OLT to HIDA			
Days [median (range)]	8 (3–51)	10 (5–60)	0.132
Donor information			
Age (years) [median(range)]	51 (19–74)	57 (38–58)	0.379
BMI [median (range)]	24 (18–36)	27 (21–34)	0.314
CIT [median (range)]	572 (401–1032)	490 (458–659)	0.177
WIT [median (range)]	56 (35–96)	39 (18–58)	0.010

AST aspartate aminotransferase, *ALT* alanine transaminase, *INR* international normalized ratio, *OLT* orthotopic liver transplantation, *BMI* body mass index, *CIT* cold ischemia time, *WIT* warm ischemia time

Table 5 Incorrect HIDA scans ($n = 7$)

Report	Final diagnosis	Bilirubin
No leak	Leak, observed in the operating room	8.1
No leak	Leak, detected by ERCP	5.8
No leak	Leak, detected by ERCP	12.7
Inconclusive	Intact anastomoses	7.7
Inconclusive	No eventful outcome	29.8
Inconclusive	No leak detected by ERCP	16.1
Inconclusive	No eventful outcome	1.3[a]

[a] This HIDA scan was inconclusive due to roux en Y

Table 6 Comparison for total bilirubin (TB) above and below 5 mg/dl

TB (mg/dl)	Correct (n)	Incorrect (n)	Sensitivity (%)	Specificity (%)
>5	10	6	62.5	100
<5	17	1	100	100
Overall	27	7	70	100

p value = 0.029 for correct versus incorrect diagnosis of TB >5 mg/dl and <5 mg/dl

a biliary complication rate of 16.5%. Biliary leaks and strictures are the most common, but obstruction, hemobilia, infection, aneurysm, cystic duct mucoceles, post transplant lymphoproliferative disease, and sphincter of oddi dysfunction also occur [1, 15, 16]. These complications are the leading causes of abnormal liver function in the first 3 months after transplantation [1].

Extrahepatic drains placed at the time of surgery aid in detecting biliary complications. They allow serum bilirubin ratios to be followed. A ratio >5 may be sensitive and specific for the detection of bile leaks, and therefore selective for further workup [17].

The use of T-tube versus no T-tube for the management and prevention of biliary complications is controversial. T-tubes provide direct access to the biliary tree. Bile output and quality can be easily assessed, and cholangiographic studies easily obtained. They lower the pressure in the biliary system, and may protect the anastomosis from leaking due to decreasing intraductal pressure. Late anastomotic biliary strictures and their need for surgical repair are also reduced [1, 2]. They do not, however, prevent suture-related insufficiencies or their ischemic-related stenosis. Despite these benefits, complications from T-tubes can result in severe morbidity and mortality.

One complication is biliary leak after T-tube removal, which may lead to biliary peritonitis and cholangitis [2]. Other complications directly related to the T-tube are dislodgement and biliary obstruction. Sixty percent of complications related to T-tubes are reported to be directly related to the T-tube itself [2]. Direct T-tube cholangiography is an excellent way to assess for biliary strictures and leaks [18]. However, it is expensive, invasive, and there have been reports of bile duct injury related to chemical irritation [2].

There are a number of ways to assess for biliary complications with radiographic imaging. These can be noninvasive or invasive and include US, computed tomography/computed tomography angiography (CT/CTA), HIDA, MRCP, and ERCP. These are used alone or in combination to determine a diagnosis. Each has its benefits and limitations. The US is noninvasive and has a high sensitivity and specificity for detecting postoperative hepatic artery thrombosis and stricture [18]. However, it provides only limited evaluation of the biliary tree and anastomosis, and has a low sensitivity (54%) for detecting biliary complications [1, 18]. CT/CTA is useful for detecting vascular abnormalities, hemorrhage, and abscesses, and is often used when US is inconclusive. However, it does not always detect bile leaks or biliary strictures, especially when biliary dilatation is absent. MRCP allows for detailed and panoramic imaging of the biliary tract and has the potential to demonstrate the site, type and degree of complications as reliably as those provided by direct cholangiography by allowing total visualization of extra hepatic bile ducts and the biliary anastomosis [19]. However, it is costly, time consuming, requires the patient to be both transported and still for a long period of time, and is frequently negatively affected by artifact. ERCP is a safe procedure which has the potential to improve the range of diagnostic and therapeutic opportunities for post-OLT biliary complications in patients with a choledochocholedochostomy, including resolution of anastomotic stricture, biliary stones, and T-tube-related complications [19]. However, complications can be more severe and routine use in OLT patients is not recommended due to the high risk of cholangitis and pancreatitis.

HIDA scans are sensitive and specific tests for BC. In fact, they are considered the most sensitive noninvasive test for detecting bile leaks [18]. Al Sofayan et al. [20] reported a sensitivity and specificity in the detection of bile leaks of 100 and 77%. We report similar rates in our cohort.

After intravenous injection, HIDA is actively transported from the blood in the transplanted liver sinusoids into the hepatocytes. It is actively excreted into bile canaliculi and flows successively into the hepatic ducts, CBD, and small bowel. Thus, imaging the biodistribution of Tc-99m-radiolabeled HIDA compounds with a gamma camera, bile flow is evaluated and leakage, stricture, and obstruction were detected. HIDA scans detect bile leaks as a collection of radiotracer in a nonphysiologic space, and are an effective method for the diagnosis of biliary leaks after T-tube removal [2, 4]. This is established through

comparison of radiotracer counts in the leak with those in the bowel region [20].

We chose to use HIDA scans in some postoperative OLT patients due to their noninvasive nature, particularly in patients in the early postoperative period, and those in whom no T-tube was placed. All of our patients received a HIDA scan early after surgery (Table 2). Both donor demographics (Table 1) and our cohort demographics (Table 2) were similar to our institution's larger OTX population.

HIDA scans gave a correct diagnosis in 27 of our patients. The scan correctly diagnosed 5 biliary leaks, 3 biliary obstructions, no biliary stricture, and 19 patients without biliary complication (Table 3). The median TB for correct diagnosis was 2.4 (0.6–14.4) mg/dl. A higher TB of 8.1 (1.3–29.8) mg/dl was observed in the 7 patients with an incorrect diagnosis (Table 4). We found the difference in TB to be significant ($p = 0.003$) when comparing correct versus incorrect diagnosis. However, we had difficulty finding a correlation specifically between TB and the use of HIDA scans in liver transplant recipients in the literature.

Seven patients had an incorrect HIDA diagnosis (Table 5). Three reports indicated no leak, yet a leak was observed in surgery or by ERCP. Each of these patients had a TB >5 mg/dl. Four patients had an inconclusive report, and an uneventful outcome. Three of these had a TB >5 mg/dl, and one <5 mg/dl. Three patients with an inconclusive result, including the patient with a TB <5 mg/dl, underwent a Roux-en-Y. One had a FN HIDA, but was determined to have biliary complications. Two patients had inconclusive/nondiagnostic results. One was due to no delayed images. We believe the other, who also had the TB <5 mg/dl, was inconclusive due to the Roux. Both were followed clinically with resolution of biliary complications. We performed HIDA in patients with Roux limbs to avoid potential bleeding complications from transhepatic cholangiography and/or operative intervention. HIDA has been shown to be useful in the diagnosis of obstruction and retention in Roux-en-Y hepaticojejunostomies after liver transplantation [14, 18]. HIDAs are a safer imaging modality in Roux-en-Ys because they are noninvasive. However, they may simulate a biliary leak in blind end of the limb [18].

When analyzing patient demographics and laboratory values compared with correct and incorrect diagnoses (Table 4), we found no differences in age, gender, ALT, INR, CIT or time of OLT to HIDA scan. However, a difference was found in AST, TB, and ethnicity in the recipients, and WIT in the donors. We could not find the AST cutoff point at which HIDAs would be less useful. This may be due to the extreme range of the AST values. The median WIT was higher among patients with correct HIDA diagnosis compared to patients with incorrect HIDA diagnosis. The explanation for this finding is unclear and is likely due to small number of patients reviewed. The same is likely for ethnicity.

A high bilirubin can be a marker for hepatic dysfunction, meaning the hepatocytes are not transporting HIDA correctly into the bile canaliculi. Without adequate flow, the physiologic pathway is not optimally imaged, thus potentially decreasing the sensitivity of the imaging. In our study, when the total bilirubin was higher than 5 mg/dl, the sensitivity fell to 62.5% (Table 6). The number of FN exams increased rendering the results nondiagnostic/inconclusive and therefore less reliable. The specificity stayed at 100%. Similarly, we found HIDA scans to be an effective means of diagnosing biliary complications when the total bilirubin was <5 mg/dl, with a specificity and sensitivity of 100% with no FPs. These findings are similar to those found in nontransplant biliary pathology [3].

A current larger unpublished study at our institution reviews post-OLT biliary complications evaluated by ERCP, and encompasses some of our study population. This study found the overall biliary complication out of 594 OLT in 562 patients to be 98 (16.5%). Complications were reported as stricture, leak, cast syndrome, sludge, stones, or a combination thereof. There were 3 bile duct kinks, not associated with the anastomotic site. Biliary complications secondary to hepatic artery thrombosis were found in 12.3%. Half occurred within the first 3 months. Biliary complications occurred at the anastomotic site in 91.8%. Eighty-one were resolved with ERCP, 16 were resolved in surgery.

The rates of stricture, leak, and obstruction in our cohort were 0, 5 (14.7%), and 3 (8.8%), compared to our institution's 594 OLT biliary complication rates of 53 (8.9%), 49 (8.2%), and 10 (1.7%). Our rates are different perhaps due to the small cohort size and difference in diagnostic modality. Our study used HIDA while the larger study used ERCP.

Limitations of this review include its retrospective nature, small patient numbers spread over a long time period and the lack of a control group. There is a possibility that some leaks were labeled as inconclusive or nondiagnostic and resolved on their own without intervention.

Conclusion

We found that HIDA scans had a high sensitivity and specificity in detecting biliary complications in OLT when the total bilirubin was <5 mg/dl. When the total bilirubin exceeded 5 mg/dl, specificity was still 100%. However, the number of nondiagnostic/inconclusive and FN exams was increased. Clinicians may consider eschewing HIDA scans in the setting of hyperbilirubinemia to save time and

expenses. However, HIDA scans remain an important test in the evaluation of early BC if the TB is <5 mg/dl.

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