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ORIGINAL ARTICLE

The role of ^{99m}technetium-labelled hepato imino diacetic acid (HIDA) scan in the management of biliary pain

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Abstract

Objective. To assess the outcome of laparoscopic cholecystectomy on the basis of an abnormal provocative ^{99m}technetium-labelled hepato imino diacetic acid (HIDA) scan for patients with typical biliary pain and normal trans-abdominal ultrasound (TUS) scan. *Patients and methods.* Prospective data were collected for 1201 consecutive patients with typical biliary symptoms. Patients who were found to have a normal TUS and upper GI endoscopy subsequently underwent cholescintigraphy (HIDA scan). Patients with an abnormal HIDA scan, i.e. <40% ejection fraction with Sincalide® (cholecystokinin octapeptide) – were offered cholecystectomy. Symptoms and histology were reviewed postoperatively. *Results.* In all, 48/1201 (4%) patients with typical biliary symptoms had a normal ultrasound and endoscopy; 35/48 patients had an abnormal provocative HIDA scan and all underwent laparoscopic cholecystectomy. Histology in all cases revealed chronic cholecystitis and 18 patients had sludge or microlithiasis within the gallbladder. At 6-week follow-up, 31 of the 35 patients were completely asymptomatic or improved. Furthermore, 79% of patients remained symptom-free or improved at a median follow-up of 28.5 months (range 4–70). *Conclusions.* HIDA scan is a useful clinical tool as an adjunct to the diagnosis and management of patients who present with typical biliary pain and a normal TUS scan.

Key Words: *HIDA scan, laparoscopic cholecystectomy, biliary pain*

Introduction

Symptoms from gallbladder pathology are a common cause of surgical admissions. Trans-abdominal ultrasonography (TUS) is the standard investigation for the detection of gallstones [1]. Patients with typical biliary pain but a normal TUS scan are often under-investigated. TUS for cholelithiasis is recognized to have a false negative rate of 2–5%, with reduced sensitivity for the detection of very small stones and choledocholithiasis. In addition, the concepts of acalculous cholecystitis or gallbladder dyskinesia have been described for many decades [2,3]. Gallbladder spasm, distension or mal-coordination between contractions in the gallbladder, cystic duct and sphincter of Oddi may cause pain. Biliary stasis as a result of gallbladder dysmotility may result in chemical irritation and chronic inflammation of the gallbladder wall. Evidence for the benefit of cholecystectomy for those with biliary colic but without stones was first reported by Whipple in 1922, with 76% symptom resolution on long-term follow-up [4].

The options for further investigation of patients with typical bilary symptoms but a negative TUS include endoscopic ultrasonography and radionucleotide scanning. Endoscopic ultrasonography demonstrates increased sensitivity over trans-abdominal scanning for structural abnormalities such as gallbladder sludge, microlithiasis and choledocholithiasis. The provocative oral cholecystogram [5] led the way to dynamic assessment of gallbladder function, with provocative radionuclide cholescinthigraphy being preferred more recently [6–11]. Radionuclide scanning using ^{99m}technetium-labelled hepato imino diacetic acid (HIDA) has been available for over a decade but its use in diagnostic work-up of patients with biliary symptoms has not yet become routine

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[7–9]. Provocative HIDA scan with infusion of cholecystokinin octapeptide is preferred in most units, although the rate of infusion has been different in most published literature with various authors preferring anything from 3 to 30 min [12–14].

This study reviews the value of HIDA scan in the assessment of patients with biliary pain and their outcome after laparoscopic cholecystectomy.

Patients and methods

From October 1998 to June 2005, 1201 patients with typical biliary symptoms were referred to the Hepatobiliary Unit of St James's University Hospital, Leeds. Patient data were prospectively entered on a database. All patients were initially investigated by TUS. Patients with demonstrable cholelithiasis on TUS underwent laparoscopic cholecystectomy. If the TUS did not show any gallstones, sludge, thick wall or dilated ducts, alternative upper gastrointestinal pathologies were excluded by endoscopy.

If both the TUS and the endoscopy were normal, a provocative HIDA scan was performed (Figure 1). Dynamic acquisition of images over 180 frames at 15 s each was performed. Normal saline was injected as a control between frames 11 and 30, and 1.4 μg Sincalide® (cholecystokinin octapeptide or CCK-OP) was administered by slow intravenous injection over a duration of 5 min between frames 50 and 70. The duration of 5 min has been used in our institution based on our normal ranges on outcomes for 20 years. Gallbladder emptying was assessed and the gallbladder ejection fraction (GBEF) was calculated. Patients with an abnormal HIDA scan, defined as GBEF $<40\%$ with CCK-OP, were offered cholecystectomy (Figure 2). Patients with a normal HIDA

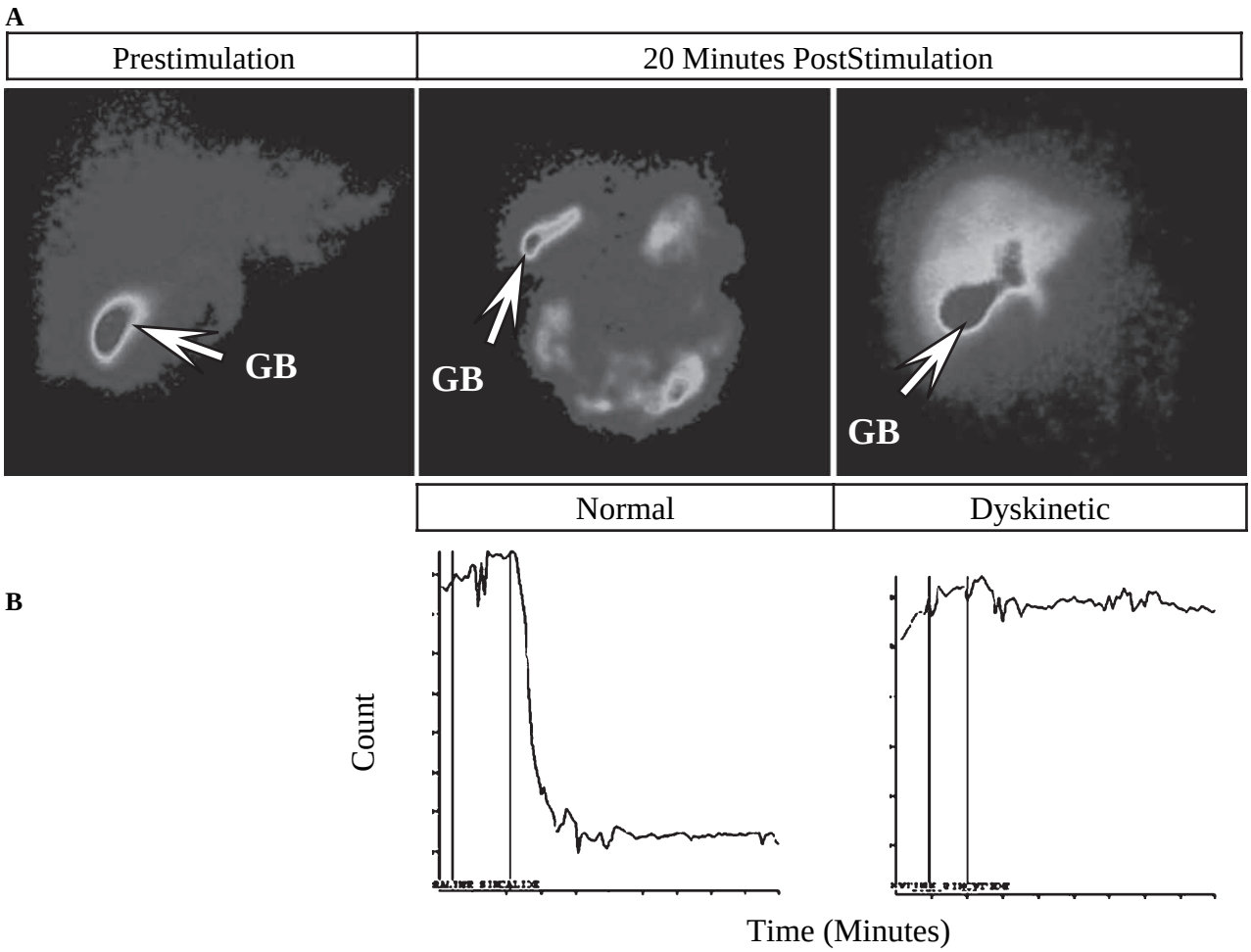

Figure 1. Cholescintigraphy using 99mHIDA to demonstrate gallbladder ejection fraction (GBEF). (A) Initially 99mHIDA accumulates in the gallbladder (GB) prior to stimulation with cholecystokinin-octapeptide (CCK-OP). A normal response shows complete gallbladder emptying with efflux of 99mHIDA into the small intestine 20 mins after stimulation with CCK-OP. Dyskinesia of the gallbladder results in pronounced retention of 99mHIDA in the gallbladder despite stimulation with CCK-OP. (B) Response curves generated by quantitation of 99mHIDA levels in the gallbladder. In the normal gallbladder, the radionuclide count rapidly decreases over the gallbladder after administration of sincalide and the fraction that has been ejected is expressed as a percentage of the initial radionuclide count. In the dyskinetic gallbladder, the administration of sincalide fails to result in ejection of the 99mHIDA even after 40 minutes. Quantitation of 99mHIDA levels in the gallbladder after stimulation with CCKOP are used to calculate the GBEF, with significant abnormality in response resulting in a GBEF $<40\%$.

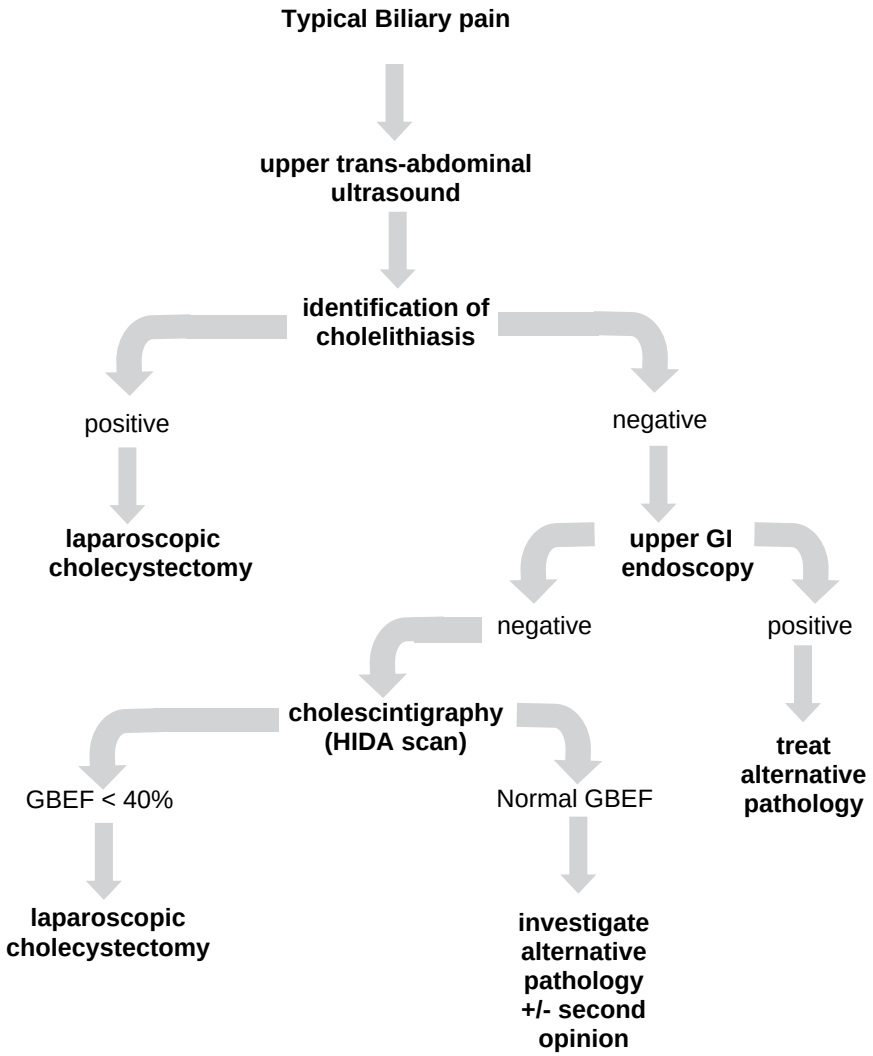

Figure 2. The investigation and management of biliary pain. The absence of cholelithiasis on investigation of typical biliary pain by trans-abdominal ultrasound should prompt investigation into alternative upper GI pathology by endoscopy. Cholescintigraphy is then performed to assess gallbladder ejection fraction (GBEF). Patients with GBEF <40% should undergo laparoscopic cholecystectomy.

scan were referred to medical gastroenterology and only re-assessed by the surgical team if their symptoms failed to resolve.

Patients who were offered laparoscopic cholecystectomy were clinically reviewed postoperatively at 6 weeks by the senior author. All patients were contacted by telephone in October 2005 by authors, S.F. and C.R.C., for a clinical review to re-evaluate symptoms. Patients were asked whether their symptoms were completely resolved, improved or unchanged. If unchanged they were asked whether an alternative diagnosis or treatment had been given (Table I).

The histology of the post cholecystectomy gallbladders was assessed by a specialist hepatobiliary pathology team. The results were compared with the histology of a historical cohort of 20 gallbladders removed as part of routine hepatectomy or liver graft implantation as a negative control, again reviewed by the same hepatobiliary pathology team. The pathologists were aware of the clinical diagnosis in all cases, including the control group.

Results

Forty-eight patients (4%) had no gallstones on TUS and a normal upper gastrointestinal endoscopy and subsequently underwent HIDA scanning.

Outcome after laparoscopic cholecystectomy in patients with GBEF <40%

Thirty-five patients (10 male, 25 female; median age 46 years, range 17–80) had a GBEF <40% and

Table I. Questions for assessment of continued symptoms during follow-up.

Questions asked at follow-up
Do you have any abdominal pain?
Is it the same pain that you had before your operation?
If yes – Is it better, the same or worse than the pain before your operation?
If no – Have you seen any other doctor about the pain?
Have you been given another diagnosis for the pain?
Have you had any other treatment for the pain?

subsequently underwent laparoscopic cholecystectomy. All patients had normal liver function tests preoperatively. Routine peroperative cholangiogram was performed in all except one patient who was known to have contrast allergy. All operations were successfully completed laparoscopically.

At 6-week clinic review, 31 of the 35 patients reported significant improvement in their symptoms, and 27 patients were completely symptom-free. Four patients remained symptomatic. All patients were contacted by telephone in October 2005 for re-assessment (median follow-up of 28.5 months, range 4–70). Six patients were lost to follow-up and one patient died due to disseminated colonic carcinoma 15 months after laparoscopic cholecystectomy. These seven patients were symptom-free at the 6-week clinic review. Of the remaining 28 patients, 22 patients reported improvement, with 19 completely asymptomatic. Six patients reported continued symptoms, five of whom had also reported continued symptoms at the 6-week clinic review. Two of these patients were finally diagnosed with irritable bowel syndrome and four continue to be investigated including assessment for sphincter of Oddi dysfunction.

Eighteen patients with a GBEF $<40\%$ on HIDA scan had evidence of sludge or microlithiasis at operation. All post cholecystectomy gallbladders showed histological evidence of chronic cholecystitis compared with the negative control group, which all had normal histology except for one with mild chronic cholecystitis.

Outcomes in patients with GBEF $>40\%$

Thirteen patients had GBEF $>40\%$ on HIDA scan. These patients were referred to medical gastroenterology and were also followed up by telephone clinical review. Four patients reported spontaneous improvement in their symptoms. Nine patients reported continued biliary symptomatology, of whom six have subsequently undergone laparoscopic cholecystectomy with full resolution of their symptoms. All six gallbladders demonstrated histological evidence of chronic cholecystitis. One patient (with co-morbidities of hepatitis C, cirrhosis and varices) re-presented with acute cholecystitis and eventually underwent open cholecystectomy.

Discussion

Prior to the discovery of oral cholecystography (OCG) by W.H. Cole [5] in 1923, surgeons relied on symptomatology to make a decision to remove the gallbladder. Oral cholecystogram proved to be beneficial in identifying symptomatic gallbladders. Gallstones, polyps, adenomyosis and occasionally cancer could be visualized in the opacified gallbladder [15] and the persistence of gallbladder opacification after 24 h was considered an indication for cholecystectomy [16]. Subsequently the cholecystokinin provocation test [2] was used to reproduce biliary colic as a pharmacodiagnostic agent in those with no convincing stones on OCG, but its efficacy was found to be questionable [17]. Cholecystokinin stimulation has been used in conjunction with both OCG and dynamic ultrasound scan [18] but the standardization of results has proven difficult [19]. Freeman et al. combined this with duodenal bile analysis to create a protocol for cholecystectomy based on poor emptying of gallbladder and presence of supersaturated bile [20]. Biliary excretion studies using ^{99m}technetium-labelled HIDA, with subsequent provocation either with cholecystokinin analogue or various forms of fatty meal, have been used since the late 1970s [6–9,21]. The major advantages of such studies over other investigations of gallbladder function are their reproducibility and lack of operator dependence [10]. There is no consensus regarding the duration of infusion, with various authors preferring anything from 5 min to 60 min based on personal experience [12–14]. Reproducibility studies with various doses and duration of infusion are few in the literature [22], but with no clear-cut indication as to the optimum duration or ideal dose. Our experiences with the 5 min infusion have been that it avoids the high peak of serum concentration leading to the unreliable response often seen with bolus infusion and with no disadvantages compared to the 30 min infusion.

While HIDA scan is accepted as an accurate and reproducible method of demonstrating gallbladder dysfunction or dyskinesia, there is currently no consensus regarding the level of dysfunction (indicated by the ejection fraction or GBEF) at which cholecystectomy may be reliably beneficial. Clinical improvement after cholecystectomy in patients with gallbladder dysfunction has been demonstrated by a number of studies, but the use of a variety of doses and administration regimes of CCK-OP makes comparison between these studies difficult to interpret and subsequent definitions of abnormal GBEF vary between 35 and 65% [23]. In this study, a GBEF of $<40\%$ was used, corresponding to levels defined by the Rome II Committee on Biliary Dyskinesia. Although CCK-OP infusion has been associated with reproduction of biliary colic, there is evidence that this is not reliable [12,13,24] and hence we have not attempted to correlate the reproducibility of clinical symptoms with infusion of CCK-OP.

HIDA scan has so far been used predominantly to diagnose dyskinetic gallbladder in those deemed to be acalculous on ultrasound scan. Accuracy of TUS scan is operator- and patient-dependent, with a reported false negative rate of 2–5% and reduced sensitivity for choledocholithiasis and the presence in the gallbladder of sludge or calculi smaller than 3–5 mm. Endoscopic ultrasound demonstrates increased sensitivity for structural disease but may also be operator-dependent and gives no indication of gallbladder

function. Dill et al. [25] reported the identification of microlithiasis or biliary sludge by endoscopic ultrasound in 58 out of a series of 66 patients (88%) who had typical biliary symptoms and negative TUS. In the study presented here, half the patients with abnormal HIDA scans demonstrated sludge in the gallbladder at operation and this is consistent with other studies documenting abnormal gallbladder motility in the presence of gallstones [26–29]. However, half of the patients with documented gallbladder dysmotility on HIDA scan in this study had no evidence of biliary sludge and would have not benefited from endoscopic ultrasonography.

All gallbladders in this series with or without sludge showed evidence of chronic cholecystitis, while others have reported a 70–90% incidence of chronic cholecystitis in similar series [30–35]. The aetiology of the chronic inflammation in these gallbladders is unclear. Gallbladder dysfunction causing biliary stasis is thought to contribute to chronic cholelithiasis in up to 70% of patients with symptomatic disease and is confined to cases where bile is supersaturated with cholesterol. Excess cholesterol incorporates into the plasma membrane of the smooth muscle cells in the gallbladder wall affecting muscular contractility with the resulting biliary stasis and cholelithiasis (macro- or microscopic) causing chronic inflammation. Conversely, the inflammatory process itself, acute or chronic, may contribute to dysfunction of the muscular gallbladder wall. There are conflicting reports regarding the proportion of histologically inflamed gallbladders in asymptomatic acalculous gallbladders. Our review of control gallbladders showed that only 1 of 20 showed any sign of inflammation and therefore suggests that the universal pathological inflammation reported in this study is related to symptoms in both the HIDA-positive and -negative patients.

In this study, 89% of patients with an abnormal HIDA scan had symptomatic relief or improvement at 6-week clinic review. Seven patients were lost to long-term follow-up (including one death) but were all asymptomatic at 6 weeks. In all, 79% of the remaining patients were asymptomatic or improved at long-term follow-up. This study also provides limited evidence, corroborated by other reports in the literature [23,37], suggesting that some patients with typical biliary symptoms and normal HIDA scan may also benefit from cholecystectomy. However, all these studies have followed very small numbers of patients. Patients with typical biliary symptoms and a negative ultrasound, endoscopy and HIDA scan require extensive investigation and a period of observation before committing to this course of action.

This is the largest reported series in the UK of patients undergoing cholecystectomy on the basis of an abnormal HIDA scan. The results compare favourably with other international studies [30–36,38] and show that the HIDA scan is a very useful tool in early diagnosis of biliary pain in those patients who have a normal TUS scan. HIDA scan provides the clinician with a simple, reproducible, non-invasive and objective test before proceeding with surgery.

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