Patient selection for cholecystectomy based on oral fatty meal augmented cholescintigraphy in cases with chronic acalculous biliary pain: Is it really that reliable?

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ABSTRACT

Background: Gallstones disease associated with biliary symptoms such as gallbladder dyspepsia (epigastric discomfort, flatulence, intermittent nausea with fat intolerance), and biliary colic (abdominal pain localised in the right upper quadrant) is commonly treated by cholecystectomy. In contrast, biliary symptoms in the absence of gallstones (acalculous biliary symptoms, ABS) often constitute a diagnostic and management challenge. Decision to recommend cholecystectomy to patients with ABS is sometimes based on abnormal cholescintigram, indicating biliary dyskinesia. Recently, the radiological protocol has changed from using intravenous stimulant to oral fatty meal to augment gallbladder contraction.

Objectives: To determine the long-term outcome of patients with ABS who underwent cholecystectomy based on abnormal cholescintigraphy using a new radiological protocol of oral fatty meal augmentation of the gallbladder.

Methods and Statistical analysis: A retrospective study of cholecystectomy was undertaken of all patients with ABS who were investigated with a fatty meal-augmented hepatic iminodiacetic acid (HIDA) scans between 1998 and 2001. Their case notes were reviewed. Pearson chi-squared test (SPSS Version 10.0.7 standard Version. SPSS incorporated 1989–1999) was used to analyse the relation between various parameters.

Results: Overall, 43 patients had HIDA scans. About 37 out of 43 (86%) patients had abnormal cholescintigrams, but only 25 were recommended surgery. Four patients were excluded owing to cholelithiasis. Sixteen patients (64%) were considered cured 6 weeks later. However, nine (36%) patients failed to improve with surgery after an average follow up of 33 weeks. Out of the 12 patients with abnormal HIDA scans who were managed conservatively, 5 (42%) recovered spontaneously, and 7 (58%) remained unchanged.

Conclusion: Oral fatty meal augmented HIDA scans may be helpful in selecting patients with ABS for surgery. However, surgeons should be cautious of a potentially high false-positive rate, leaving at least a third of patients with persistent pain after surgery.

Key words: Acalculous biliary disease, Cholescintigraphy, Laparoscopic cholecystectomy

INTRODUCTION

Biliary symptoms are often described as a complex group of symptoms. Some of the common complaints are gallbladder dyspepsia (epigastric discomfort, flatulence, intermittent nausea with fat intolerance) and biliary colic (abdominal pain localised in the right upper quadrant). When biliary symptoms are associated with cholelithiasis, the treatment of choice is usually cholecystectomy. However, patients with biliary symptoms described earlier, but in the absence of gallstones on ultrasonography (acalculous biliary symptoms, ABS) represent a complex...
group in whom there may be multiple underlying causes for their symptoms. ABS can also be mimicked by nonbiliary conditions such as the irritable bowel syndrome, chronic hepatitis, gastro-oesophageal reflux disease, peritoneal adhesions, irritable bowel syndrome, musculoskeletal or right-sided pulmonary disease. Unlike patients who have gallstones and present with calculous cholecystitis, patients with ABS often constitute a diagnostic and management challenge. The main difficulty lies within selecting the group of patients who will have good response to surgical treatment. The outcome of cholecystectomy in patients without evidence of gallstones or acute cholecystitis is variable. Sometimes, a proportion of patients continue to experience abdominal pain postoperatively. Therefore, the decision to operate on these patients should be carefully based on the clinical findings and results of investigations such as cholescintigraphy.

Amongst patients with ABS, there is evidence to suggest that a demonstrable abnormal gallbladder ejection fraction (GBEF) of less than 35% can be predictive of successful surgical outcome. Technological advances have enabled the outline of a gallbladder to be imaged using intravenous radiolabelled agents like hepatic iminodiacetic acid (HIDA), and the GBEF to be measured in response to a simultaneously administered intravenous agent. Conventionally, intravenous cholecystokinin (CCK, or its active octapeptide, CCK-OP), is used as a gallbladder stimulant in many centres. The efficacy of GBEF derived from CCK-HIDA scan in predicting successful surgical outcome has been reported in the literature to be high as 95%. However, there has been a decline of interest in using an intravenous gallbladder as stimulating agents, and in many centres standardised oral fatty meals are administered instead as a mean of stimulating gallbladder contraction during HIDA scan. This change has partly been due to potential side effects seen with intravenous agents. Furthermore, other stimulating agents such as oral fatty meal is being increasingly recommended because of its more physiological status. In addition, oral fatty meals are easily handled by untrained department staff, and are considerably less expensive. However, the use of fatty meal has mainly been validated almost exclusively in healthy subjects and consequently, this practice has been criticised.

The complexity of biliary dyskinesia or ABS combined with a growing familiarity amongst surgeons in laparoscopic techniques therefore underscores the need for diagnostic accuracy. In accordance to recent trends, our unit changed from using intravenous CCK to oral fatty meal gallbladder augmentation. Therefore, we wished to determine the clinical and histopathological outcome of this group of patients with ABS who had undergone surgery based on abnormal HIDA scans using a new radiological protocol (oral fatty meal augmentation)

MATERIALS AND METHODS
Patient selection for treatment and assessment
Patients who underwent HIDA scans between 1998 and 2001 were retrospectively identified, and their case notes were reviewed. Relevant clinical details were retrieved systematically using a predetermined proforma questionnaire. HIDA scans were carried out in patients who have biliary symptoms such as gallbladder dyspepsia (episgastric discomfort, flatulence, intermittent nausea with fat intolerance), biliary colic (abdominal pain localised in the right upper quadrant), but with no evidence of gallstone disease on ultrasound scan. The decision to consider surgery was based on an abnormal HIDA scan (GBEF of <35%), severity of symptoms, exclusion of nonbiliary factors that could mimic ABS, and patients’ choice with full counselling for risks of surgery involved. Patients who were not fit for, or who decline surgery were used as controls. Cholecystectomies were performed using standard laparoscopic techniques in all patients. Postoperative clinical outcome was assessed as previously described by others. Each case was considered a therapeutic ‘success’ if preoperative symptoms resolved entirely or improved to such an extent that it no longer interfered with daily living. Inversely, if the patient had significant and persistent or new symptomatology and required further investigations, it was considered a therapeutic ‘failure’. Symptoms were judged according to the same criteria in the nonoperated group.

All gallbladder specimens were examined using standard haematoxylin and eosin immunostaining techniques. They were grossly inspected for stone content and wall thickness; sections were examined for hyper trophy, Rokitansky–Aschoff sinuses, mononuclear infiltration, metaplasia, fibrosis, and other signs of chronic inflammation. The presence of cholelithiasis excluded the related patient from the study. Postoperative clinical success in the presence of normal gallbladder histology was considered diagnostic of biliary dyskinesia.

Oral fatty meal augmented HIDA scan
Cholescintigraphy was performed following an overnight fast. One-hundred MBq of 99 mTc-Mebrofenin [N-(2,4,6-Trimethyl 3 Bromophenyl carbomoyl-methyl) iminodiacetic acid, that is, Trimethyl-bromo-IDA or Hepatic IDA (HIDA) scan] was administered intravenously (Cholecis® Kit, CIS bio International, Schering Health Care Ltd., The Brow, Burgess Hill West Sussex, RH15 9NE). Imaging with a low-energy general purpose collimator positioned over the supine patient was commenced after 30 min. The acquisition time was 15 s per 128 x 128 element frame, and activity was
recorded with a single-headed Elscint Apex SPX6HR gamma camera (Elscint Ltd., 13 Noah Mozes St., Tel Aviv 67442, Israel). A region of interest (ROI) was drawn around the gallbladder according to the distribution of activity. A similar ROI was drawn around an adjacent area of the liver to determine background counts. Scanning data was recorded in an Elscint Apex SPX1 NM Workstation. Corrections for radioactive decay were made by the workstation. At the time of peak gallbladder activity (as determined in a quantitative time–activity curve), or at most 60 min after the administration of radioisotopes, an oral fatty meal challenge was given (Kit-Kat® chocolate bar, 10.6 g fat content, total weight 48 g). Scanning continued for 25 min after ingestion. GBEF was calculated according to the formula $\text{GBEF} = \left(\frac{\text{Activity}_{\text{max}} - \text{Activity}_{\text{contracted}}}{\text{Activity}_{\text{max}}}\right)$, where 0.35 or more was considered normal. No adverse clinical response to the fatty meal challenge was recorded during scanning.

### RESULTS

#### Basic cohort data

During the review period, 52 patients had HIDA scans for clinically suspected chronic acalculous biliary disease. Four patients were lost to follow up and six other patients were subsequently excluded due to a diagnosis of cholelithiasis was made at surgery (prior ultrasound scans were negative for gallstones). Forty-two patients were included in the study. The average GBEF was 0.19 (range 0 – 0.59). Out of the 42 patients, 37 (88%) were found to have abnormal HIDA scan (GBEF < 0.35). The average age was 43 years (range 20 – 68). One operation was converted to an open procedure, and one emergency laparotomy was undertaken postoperatively because of an intra-abdominal haemorrhage. About 5 of 42 patients had normal HIDA scan and elected to have no surgery after being counselled for risk of therapeutic failure [Figure 1].

#### Analysis of clinical outcome

Amongst patients who had surgery, two-thirds of those operated [16 (64%), mean GBEF = 0.16] were noted to achieve therapeutic success. This group was followed up as outpatients for an average of 42 days. However, nine patients (36%, mean GBEF 0.13) failed to improve with surgery despite a mean postoperative follow up of 33 weeks. As for patients who did not undergo any operations, seven remained unwell (58%, mean GBEF 0.2) but five recovered spontaneously (42%, mean GBEF 0.11), after an average follow up of 45 weeks. Interestingly, out of five patients found to have normal HIDA and elected to have no surgery, 1 (20%) case was subsequently found to have peptic ulcer disease. The other 4 (80%) cases became asymptomatic after a period of 12 months. No gastric or abdominal pathology were found in these four patients [Figure 2].

#### Histopathology

After surgery, 21 patients (mean GBEF 0.16) were found to have histopathological evidence of chronic acalculous cholecystitis (CAC). Fifteen patients with CAC (60%, mean GBEF 0.16) achieved therapeutic success. However, despite a mean follow up of 33 weeks, six patients

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* See results section (basic cohort data)

**Figure 1:** Flow chart indicating patient distribution

**Figure 2(A):** Cohort characteristics

<table>
<thead>
<tr>
<th>N</th>
<th>Mean age (years)</th>
<th>Female: Male ratio</th>
<th>Follow up (weeks)</th>
<th>GBEF *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic success</td>
<td>16</td>
<td>40.2</td>
<td>14:2</td>
<td>6.2</td>
</tr>
<tr>
<td>Therapeutic failure</td>
<td>9</td>
<td>42.9</td>
<td>9:0</td>
<td>33.2</td>
</tr>
<tr>
<td>No surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remained unwell</td>
<td>7</td>
<td>47.1</td>
<td>4:3</td>
<td>61</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>5</td>
<td>42.8</td>
<td>4:1</td>
<td>45</td>
</tr>
</tbody>
</table>

* GBEF = Average gallbladder ejection fraction
Abnormal HIDA = GBEF less than 35%

**Figure 2(B):** Clinical outcome of patients with abnormal HIDA scan

Comparison of clinical outcome according to surgery versus no surgery. Postoperative outcome was not significantly related to preoperative HIDA scan findings in patients with no gallstones ($p = 0.16, \chi^2$)
failed to improve (24%, mean GBEF 0.14). Amongst four patients with normal gallbladder histology, 1 (4%) became asymptomatic and deemed cured (GBEF 0.12, biliary dyskinesia). However, three (12%) failed to improve after follow up of 25 weeks (mean GBEF 0.093). Out of nine cases, who did not achieve therapeutic success, six (67%) of them has histological evidence of CAC [Figure 3].

DISCUSSION

Predictive value of oral fatty meal-HIDA scan
The present study also indicated that there is no statistically significant relation between postoperative outcome and oral fatty meal-HIDA scan. Furthermore, the therapeutic success rate is only just above 50%, which is relatively low. This low rate may have been owing to potential inherent methodological imaging flaw, causing inclusion of false positives. HIDA imaging is not without its criticisms. Gallbladder performance is known to depend on factors such as medication, hormones, and co-existing medical conditions, which must be taken into account when interpreting the HIDA scan. The choice of cut-off for GBEF (above which, indicates a normal gallbladder emptying) greatly influences the precision of the scan: a too high threshold giving rise to false positives, and a too-low threshold to false negatives. Chen et al. used 95% confidence interval analyses to calculate the correct cut-off. Their local CCK-HIDA scan protocol accepts a threshold of 0.28 to distinguish CAC from normal gallbladders reliably.[10] Other authors have used other limits according to choice of intravenous triggering agents. Ziiessman has even reported that the rate at which the CCK infusion is given will influence the cut-off: a doubled infusion rate raising the normal GBEF from 0.30 to 0.40 according to their protocol.[2] In the transition from intravenous to oral augmenting agents, the commonly used normal threshold of 0.35 has remained the standard. No studies have evaluated the sensitivity or specificity of oral fatty meal-HIDA scans in relation to subsequent surgery. The little research done has shown that there were significant differences in gallbladder response to different types of fatty meals.[11] Therefore, we simply do not know whether 0.35 is the correct threshold to use in the selection of candidates for cholecystectomy.

Another reason why cholecystectomy based on abnormal oral fatty meal-HIDA scan has a low therapeutic success rate may have been because of the range of biliary symptoms that patients have. For example, a group of patients with right upper quadrant abdominal pain only may have a higher therapeutic success rate than a group with epigastric bloating and dyspepsia. Therefore, it would be interesting to perform subgroup analysis of therapeutic success rate on different groups of patients, where each group has the same presenting symptom. In other words, the new hypothesis is that oral fatty meal-HIDA scan has higher predictive value in a subgroup of patients who have perhaps less than one or two symptoms only. Unfortunately, due to the small number of subjects in this study, subgroup analysis results will not be meaningful and can be misleading.

Clinical outcome of nonsurgical therapy
In this study, despite evidence of abnormal gallbladder functions based oral fatty meal-HIDA scan, patients who did not undergo surgery showed a surprisingly high rate of spontaneous recovery (42%). This finding may have been due to the relatively small numbers involved. However, O’Neill and McCreath reported that 55% of the nonoperated group was either subsequently attributed to other diagnoses or resolved spontaneously.[12] Most studies reported a high rate of success but failed to evaluate the outcome of those (however small numbers they are) who remained symptomatic after surgery. We felt that this small but significant group of postoperative patients with ABS will require further evaluation so that the true benefit of using HIDA imaging (either oral fatty meal or CCK augmented) to select patients for surgery can fully be assessed.
Relation between postoperative outcome and histological finding

This study also indicated that 67% of operative failures (all based on abnormal oral fatty meal-HIDA scans) were associated with histological CAC. This finding seemed surprising because removal of histologically abnormal gallbladders should be associated with cure. This paradox may have been due to either insufficient follow up or small numbers. However, other authors have reported similar finding, with mean follow-ups ranging up to 30 months.10,13 Interestingly, by implementing a scheme for blind histopathological scoring, the number of cases of CAC reported in this group of operated failures was reduced by half.14 This suggests that histopathologists may have over-reported CAC and stricter criterion for diagnosing the condition would be more appropriate. Conversely, it may be possible that the prevalence of asymptomatic gallbladder inflammation is higher than previously anticipated. In a study on the histopathology of asymptomatic gallstones, Csendes et al. found that 33% of subjects in the control group demonstrated mucosal pathology, most commonly CAC. This finding was more common amongst older subjects.15

Length of postoperative follow up and ‘cure rate’

Radiological criteria for the diagnosis of gallbladder disease largely rest on the detection of calculi. However, in the absence of gallstones, surgeons are often reluctant to carry out cholecystectomy in patients with symptoms of gallbladder disease if the ultrasound scan is normal. Such group of patients are often left with no satisfactory treatment. This study showed that more than 60% of patients were recommended surgery, a figure that is in congruent with other published data. Unfortunately, a significant group of these patients are left with persistent abdominal pain. Evidence showed that long-period follow up may be required, if the full therapeutic effect of cholecystectomy is to be seen. We found that while a follow up of only 7 weeks was sufficient for cure to ensue in most of our patients, the remainder had derived no benefit from surgery after a mean follow up of 30 weeks. Although it is tempting to conclude that persistent symptoms after surgery will resolve in time, there is evidence that at least 5% will remain so with 6 years follow up.16 Conversely, other authors have reported satisfactory outcomes with only minimal follow up: Gunna et al. showed that abnormal fatty meal augmented HIDA scan is predictive of at least 95% success rate with 10 months of follow up.17 Barron et al. used CCK-OP augmented cholescintigraphy for patient selection, and achieve cure in as many as 100% of patients on day 10 postoperatively.18 No suggestion has been made of how long it is acceptable for patients to wait for cure to set in. If improvement is indeed due to gallbladder removal, it seems reasonable to expect symptoms to resolve not long after the surgery.

CONCLUSIONS

Management of patients with ABS is complex. We have not specifically compared the efficacy of CCK-HIDA scans with oral fatty meal: HIDA scans. Only one study compared the efficacy CCK injection with oral fatty meal during HIDA scan. The results indicated that GBEFs created by oral fatty meal are significantly lower, more variable, and ejection period is more prolonged.7 The change of radiological protocol for HIDA scan results in moderate benefits only. However, we felt that oral fatty meal-HIDA scan in patients with ABS has got a diagnostic role but it is conceivable that surgeons will tend to over-rely on this investigation in selecting patients for surgery. Although this study involved only a small number of patients, the failure rate in operating on ABS patients based on oral fatty meal-HIDA imaging is unacceptably high. In view of this, we cannot recommend surgery to ABS patients with abnormal GBEF based solely on the usage of oral fatty meal augmented HIDA scan.

REFERENCES


