Meta-analysis of Cholecystectomy in Symptomatic Patients With Positive Hepatobiliary Iminodiacetic Acid Scan Results Without Gallstones

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Objective: To study the clinical results of surgical management in patients with right upper quadrant pain, a positive hepatobiliary iminodiacetic acid (HIDA) scan result, and no gallstones.

Data Sources: Health care databases and gray literature.

Study Selection: Each article was scrutinized to determine whether it met inclusion criteria. Only abstracts, full articles, and gray literature that passed the detailed screening procedure were included. Case reports, letters, comments, reviews, and abstracts with insufficient details to meet inclusion criteria were excluded. Gallbladder ejection fraction assessed by means other than cholecystokinin HIDA scan were also excluded.

Data Extraction: Three reviewers independently abstracted the following data from each article: first author, year of publication, journal, type of study, location of study population, institution where the study was conducted, symptoms recorded, imaging modality used to establish the absence of gallstones, HIDA scan ejection fraction, number of cases and controls, number of males and females in each group, method of follow-up, and number of cases lost to follow-up.

Data Synthesis: Ten studies met inclusion criteria (N=615). Follow-up ranged from 3 to 64 months. Surgical treatment was 15-fold more likely than medical treatment to result in symptom improvement, with 4% of patients reporting no symptom improvement with surgery. Sensitivity analysis in patients with complete symptom relief following surgery revealed an 8-fold greater odds difference than those treated medically (indicating variation in study reporting).

Conclusions: Patients without gallstones who have right upper quadrant pain and a positive HIDA scan result are more likely to experience symptom relief following cholecystectomy than those treated medically. There is, however, wide variability in data reporting, particularly with respect to symptom relief and duration of follow-up. Cholecystectomy is indicated in symptomatic patients without gallstones who have a low–ejection fraction HIDA scan.


THE TREATMENT OF SYMPTOMATIC patients with evidence of gallstones is well established, with laparoscopic cholecystectomy being the treatment of choice for symptomatic cholelithiasis. Since cholecystectomy’s introduction in 1989, it is estimated that more than 700 000 of these operations are performed annually in the United States,1 with as many as 80% to 90% of patients reporting relief of long-term symptoms as a result.2 The results of surgery in symptomatic patients without gallstones are highly variable. These patients are often referred to as having biliary dyskinesia or acalculous gallbladder disease. Despite the variability of surgical outcomes in these patients, 5% to 30% of cholecystectomies performed annually are for diagnosed biliary dyskinesia.3-5 This has led to the need to better identify candidates with a specific preoperative test who will benefit from surgery. It is widely believed that hepatobiliary iminodiacetic acid (HIDA) scans can help better stratify patients who would experience better postoperative outcomes.

The evaluation of symptoms in patients with these symptoms, but without gallstones, is less clearly defined. A HIDA scan, also referred to as cholescintigraphy, assesses gallbladder function by measuring the percent decrease in net gallbladder radioactivity during a specified period after infusion of cholecystokinin (CCK). A HIDA scan is advised by the Rome II Consensus Group6 to be the next step in patient evaluation.

Patients with gallbladder disease typically present with right upper quadrant pain, epigastric and postprandial pain, nausea, and emesis. The precise association of these symptoms with gallbladder disease is not well understood and the definition of biliary pain is relatively broad.6 This symptomatology is initially investi-
gated with ultrasonography. Other modes of imaging are also used, including computed tomography, endoscopic retrograde cholangiopancreatography, and upper and lower gastrointestinal endoscopy.

There are conflicting reports of the predictive value of HIDA scans in symptomatic patients without gallstones, despite 2 recent meta-analyses that attempted to address this question.7,8 The first of these 2 meta-analyses included only symptomatic patients with abnormal (positive) and normal HIDA scan results who underwent surgery.7 The second study, by Ponsky et al,6 like ours, examined outcomes of patients with abnormal HIDA scan results who were medically treated compared with those who underwent surgery. The authors did not, however, use current guidelines and neither conducted a systematic review nor searched gray literature.

This systematic review and meta-analysis was undertaken to assess whether or not cholecystectomy is indicated in patients without gallstones who have right upper quadrant pain and a positive HIDA scan result. We hypothesize that in such patients, a positive HIDA scan result is a good predictor of outcomes.

METHODS

STUDY SELECTION

We conducted a search of MEDLINE (January 1989-March 2007), EMBASE, and Cochrane databases, using PubMed, Google Scholar, and Ovid as search engines. EMBASE is a health care database that is recognized as an important source of pharmacological and biomedical literature. It is a relevant source of negative-results studies and studies that did not reach statistical significance, as it includes European and non-English language journals that are more likely to publish inconclusive findings.3 We did not have any language restrictions and we used the following keywords: laparoscopic, cholecystectomy, cholescintigraphy, and iminodiacetic acid. Boolean operators (not, and, and or) were also used in succession to narrow and widen the search. To increase the number of hits using the Ovid search engine, we used the “Explode” and “Related Article” functions. Based on titles and abstracts, we either downloaded or requested full articles of the studies through our library. To locate unpublished material and to avoid systematic (ie, publication) bias, we manually searched the references of original and review articles and evaluated symposia proceedings, poster presentations, and abstracts from major gastrointestinal meetings.

The quality of primary studies was evaluated using the Newcastle-Ottawa Scale,12 which is a validated technique for assessing the quality of nonrandomized studies. We subjected our results to sensitivity analyses to quantitatively establish the heterogeneity of our findings.

INCLUSION AND EXCLUSION CRITERIA

Abstracts, full articles, and gray literature that passed the primary screening were retrieved and screened for the presence of the following:

- Two arms in each study. Symptomatic patients with documented evidence of no gallstones and a positive (abnormal) HIDA scan result were offered either surgical (laparoscopic and/or open cholecystectomy) or medical (primary choice) treatment. If patients subsequently underwent surgery, they were excluded from analysis.
- Symptomatic patients, defined as having right upper quadrant pain, epigastric and/or postprandial pain, nausea, emesis, and other symptoms.
- Confirmation of absence of gallstones, exclusion of structural biliary abnormalities with 1 or more imaging modalities, including ultrasonography, computed tomography, upper and lower gastrointestinal endoscopy, and endoscopic retrograde cholangiopancreatography.
- Patients with abnormal gallbladder ejection fraction (≤50%) were offered surgical and medical treatment options.
- Gallbladder ejection fraction was assessed using a CCK HIDA scan.
- Methods of collecting data included telephone interview, direct interview, and/or questionnaires.
- No stipulation on the length of follow-up.
- Degree of symptom resolution following surgery or medical treatment categorized as complete, partial, none, or worse.
- If there were multiple publications of the same study, only the most recent publication was considered for analysis.

The exclusion criteria served as a primary screening procedure to exclude the following:

- Case reports, letters, comments, reviews, and abstracts with insufficient details to meet inclusion criteria.
- Gallbladder ejection fraction assessed by means other than CCK HIDA scan.

DATA EXTRACTION

Three independent reviewers (S.S.M., N.S.J., and K.S.M.) abstracted the data. Each article was scrutinized to determine whether it met inclusion criteria. Each reviewer independently abstracted data using a standardized data collection form to ensure uniformity and reduce reporting bias. Discrepancies were resolved by consensus. Reviewers independently abstracted the following data from each article: first author, year of publication, journal, type of study, location of study population, institution where the study was conducted, symptoms recorded, imaging modality used to establish the absence of gallstones, HIDA scan ejection fraction, number of cases and controls, number of males and females in each group, method of follow-up, and number of cases lost to follow-up.

STATISTICAL ANALYSIS

We stratified the outcome variable for response to treatment as partial, complete, or none. Studies that used different terminology such as improved or asymptomatic in response to treatment were categorized as partial or complete responders, respectively. Worse outcomes following treatment were combined with the none group. We did this to increase group homogeneity and to increase the size of each patient group.

Meta-analysis was performed according to Meta-Analysis of Observational Studies in Epidemiology guidelines11 and the recommendations of the Cochrane collaboration.12 The effect measures estimated were odds ratios (ORs) for dichotomous data, which we report with their 95% confidence intervals (CIs). The OR indicates the odds of an individual with the risk characteristic of interest (ie, symptomatic, abnormal HIDA scan result, and no evidence of gallstones) improving after surgery compared with improving following medical therapy. Values greater than 1.0 indicate an improvement in symptoms postoperatively, while values less than 1 imply that surgical treatment was not beneficial. If studies contained a 0 in 1 cell for the number of events of interest in 1 or 2 groups (ie, 0 patients with partial relief in the medical therapy arm of a study), the Hal-
dane correction was applied by adding 0.5 in both groups from that study.\textsuperscript{13}

The ORs from the separate studies were combined according to a random-effects model (Mantel-Haenszel),\textsuperscript{14} which does not require the assumption that the effects found in the separate studies are the same (ie, homogeneous) or equal. Random effects are appropriate when the populations in the separate studies differ with regard to, for example, protocol, duration of follow-up, or how the risk characteristics or disease end points were measured. In general, the random-effects model is more conservative than a fixed-effects model.\textsuperscript{15,16} All analyses were conducted using Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, New Jersey).

VALIDITY ASSESSMENT

Several strategies were adopted to assess the validity of our approach. We tested for heterogeneity among studies using the Mantel-Haenszel test, with $P < .10$ used to reject the null hypothesis that ORs from the separate studies were homogeneous.\textsuperscript{17,18} In addition, the $I^2$ index was used to quantitatively measure heterogeneity between studies, which is purported to be a better discriminator of heterogeneity when the meta-analysis involves a small number of studies, each with a small sample size.\textsuperscript{18} $I^2$ values lie between 0% and 100% and are presented with a 95% CI. Increasing $I^2$ values represent increasing heterogeneity. By convention, an $I^2$ value of 50% or greater represents significant heterogeneity. We also constructed funnel plots to visually investigate for the presence of publication bias.\textsuperscript{19,20} This was followed by quantitative assessment of publication bias using the Begg and Mazumdar\textsuperscript{21} and Egger et al\textsuperscript{22} tests. The Egger et al test detects funnel plot asymmetry by determining whether the intercept deviates significantly from 0. If the CI does not include 0, then there is evidence of publication bias.\textsuperscript{22} The adjusted rank correlation test of Begg and Mazumdar assesses whether there is a significant correlation between the effect estimates and their variances.\textsuperscript{21}

Sensitivity analysis was undertaken to evaluate the stability of the association between symptom relief (eg, complete vs none, partial vs none, and any vs none) and treatment type, the study’s quality (≥6 stars on the Newcastle-Ottawa Scale), and other clinically relevant variables. The largest study was excluded in 1 of the sensitivity analyses to establish whether the large samples had a significant effect on the overall strength and direction of the results.

Our initial search yielded 686 literature citations (Figure 1). Of these, 686 citations were excluded after primarily reviewing the full-text article because they were irrelevant to biliary dyskinesia (n = 638), cholecystectomy (n = 25), or HIDA scan results (n = 5). An additional 3 review articles,\textsuperscript{7,8,27} 1 case report, 3 studies with no control arm, and 1 study with a vague description of symptom relief\textsuperscript{24} were excluded, leaving 10 randomized controlled trials eligible for meta-analysis.

Ten studies\textsuperscript{25-34} met the eligibility criteria (Figure 1) and included 462 patients who underwent cholecystectomy and 153 patients who were treated medically; they all had an abnormal gallbladder ejection fraction (positive HIDA scan result) (Table). The OR for patients with a positive HIDA scan result who were treated surgically (vs medically) with improvement of symptoms was 16.26 (95% CI, 3.82-69.19; $I^2 = 72.3$) (Figure 2).

Eight\textsuperscript{25-31,33} of 10 studies used less than 35% as the definition of an abnormal gallbladder ejection fraction, while 2 studies\textsuperscript{32,34} used less than 50%. Two studies\textsuperscript{29,30} mentioned the number of males and females in each study arm, females outnumbering the males in each study. Eight of 10 studies were conducted in the United States, while 1 study was performed in the United Kingdom,\textsuperscript{27} another in Australia.\textsuperscript{32}

Follow-up ranged from 3 to 6 months. Outcome assessment was made by direct office-based interview in only 2 studies,\textsuperscript{31,33} while telephone interviews were used in 7 studies.\textsuperscript{26-31,33} One study did not specify the method of follow-up.\textsuperscript{34}

SENSITIVITY ANALYSIS

We performed sensitivity analyses on patients who underwent surgery. These analyses were performed according to whether the patients reported that they had any, complete, or partial symptom relief.

Complete and Partial Symptom Relief

In 9 studies (n = 434),\textsuperscript{25,26,28-34} surgery was associated with a greater likelihood of complete symptom relief compared with medical therapy, with an OR of 11.57 (95% CI, 3.82-35.05; $I^2 = 66.4$) (Figure 3). One study did not have patients with partial symptom relief in the control or treatment arms and was therefore not included in the analysis.\textsuperscript{32} In the group of patients who reported partial symptom relief (n = 604, 9 studies\textsuperscript{25-31,33,34}), the benefit of surgery was not evident (OR, 0.70; 95% CI, 0.10-4.92; $I^2 = 92.5$) (Figure 4).

Largest Study Exclusion and High-Quality Studies

With exclusion of the largest study (Middleton and Williams\textsuperscript{27}) (9 studies, n = 434), the OR for any symptom relief with surgery was 10.86 (95% CI, 2.86-41.23; $I^2 = 57.4$). Examining only those studies deemed to be of higher quality (n = 418),\textsuperscript{26,29,31,33} we found that the benefit of surgery was evident (OR, 13.85; 95% CI, 2.36-106.21; $I^2 = 79.7$) in patients with any symptom relief.
Definition of Abnormal Ejection Fraction

Two of the 10 studies defined abnormal gallbladder ejection fraction as that less than 50%. After excluding these 2 studies, surgery was considered beneficial in patients with any symptom relief (OR, 17.59; 95% CI, 3.52-87.73; $I^2 = 76.1\%$) and in patients with complete symptom relief (OR, 8.68; 95% CI, 2.49-30.21; $I^2 = 69.5\%$) (n=353; 7 studies).25,26,28-31,33.

CCK Dose

In 1 study,33 a CCK dose much greater than that in the other studies was administered. After excluding this study (n=582; 9 studies), surgery was still beneficial in patients with any symptom relief (OR, 16.43; 95% CI, 3.31-81.40; $I^2 = 75.2\%$) and in patients with complete symptom relief (OR, 9.65; 95% CI, 3.11-29.96; $I^2 = 67.1\%$), excluding 2 studies (n=401; 8 studies).25,26,28,32,34.

Duration of CCK Infusion

The duration of CCK infusion was considerably longer in 1 study32 than in the other studies (45 minutes vs 2-3 minutes); in another study, the duration of infusion was not specified.33 After exclusion of these 2 studies, sur-

<table>
<thead>
<tr>
<th>Source</th>
<th>CCK Dose</th>
<th>Reduced Gallbladder Ejection Fraction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ozden and DiBaise,30 1998</td>
<td>6 0.02 3</td>
<td>$&lt;35$</td>
</tr>
<tr>
<td>Middleton and Williams,37 2001</td>
<td>95.00 (1.48-6087.66)</td>
<td>$&lt;35$</td>
</tr>
<tr>
<td>Mishkind et al,28 1997</td>
<td>253.31 (13.57-4730.09)</td>
<td>$&lt;50$</td>
</tr>
<tr>
<td>Khosla et al,26 1997</td>
<td>95.00 (0.06-44.28)</td>
<td>$&lt;35$</td>
</tr>
<tr>
<td>Watson et al,32 1994</td>
<td>253.31 (13.57-4730.09)</td>
<td>$&lt;35$</td>
</tr>
<tr>
<td>Zech et al,34 1991</td>
<td>47.46 (9.69-232.44)</td>
<td>$&lt;35$</td>
</tr>
<tr>
<td>Misra et al,29 1991</td>
<td>47.46 (9.69-232.44)</td>
<td>$&lt;35$</td>
</tr>
</tbody>
</table>

Table. Studies of Patients With Positive HIDA Scan Results Without Gallstones

<table>
<thead>
<tr>
<th>Source</th>
<th>Surgical Treatment</th>
<th>Medical Treatment</th>
<th>OR (95% CI)</th>
<th>Favors medical treatment</th>
<th>Favors surgical treatment</th>
</tr>
</thead>
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<tr>
<td>Misra et al29</td>
<td>6/6</td>
<td>2/9</td>
<td>0.17 (0.01-3.53)</td>
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<td></td>
</tr>
<tr>
<td>Zech et al34</td>
<td>58/59</td>
<td>11/11</td>
<td>47.46 (9.69-232.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watson et al27</td>
<td>9/9</td>
<td>2/9</td>
<td>1.70 (0.08-44.28)</td>
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<td></td>
</tr>
<tr>
<td>Khosla et al33</td>
<td>2/5</td>
<td>40/41</td>
<td>13.00 (0.95-178.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mishkind et al28</td>
<td>2/5</td>
<td>6/13</td>
<td>21.00 (1.21-208.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goncalves et al25</td>
<td>44/44</td>
<td>11/11</td>
<td>50.00 (2.12-208.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yost et al33</td>
<td>6/13</td>
<td>11/11</td>
<td>50.00 (2.12-208.08)</td>
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<tr>
<td>Skipper et al28</td>
<td>14/17</td>
<td>12/12</td>
<td>50.00 (2.12-208.08)</td>
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</tr>
<tr>
<td>Watson et al32</td>
<td>134/140</td>
<td>3/41</td>
<td>253.31 (13.57-4730.09)</td>
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<tr>
<td>Ozden and DiBaise30</td>
<td>38/40</td>
<td>7/8</td>
<td>47.46 (9.69-232.44)</td>
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<td>11/11</td>
<td>47.46 (9.69-232.44)</td>
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<tr>
<td>Misra et al29</td>
<td>6/6</td>
<td>2/9</td>
<td>0.17 (0.01-3.53)</td>
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</tbody>
</table>

Figure 2. Forest plot of any relief of symptoms in patients with right upper quadrant pain without gallstones (overall result). Each group analysis is based on symptom relief status of the participants. Each square in the plot indicates the point estimate of the effect (odds ratio [OR]). The diamond represents the summary OR from the pooled studies with the 95% confidence interval (CI). The point estimate is considered significant at the $P<.05$ level if the 95% CI does not include 1.
**Figure 3.** Forest plot of complete relief of symptoms in patients with right upper quadrant pain without gallstones. CI indicates confidence interval; OR, odds ratio.

<table>
<thead>
<tr>
<th>Source</th>
<th>Surgical Treatment</th>
<th>Medical Treatment</th>
<th>OR (95% CI)</th>
<th>Favors surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misra et al(^{29})</td>
<td>58/69</td>
<td>0/29</td>
<td>300.13 (17.09-5271.25)</td>
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</tr>
<tr>
<td>Zech et al(^{24})</td>
<td>56/59</td>
<td>4/11</td>
<td>32.67 (6.02-172.15)</td>
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<tr>
<td>Watson et al(^{27})</td>
<td>9/9</td>
<td>0/2</td>
<td>95.00 (1.48-6087.66)</td>
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</tr>
<tr>
<td>Khosla et al(^{32})</td>
<td>20/30</td>
<td>0/5</td>
<td>21.48 (1.08-426.68)</td>
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</tr>
<tr>
<td>Mishkind et al(^{30})</td>
<td>15/27</td>
<td>5/15</td>
<td>2.50 (0.67-9.31)</td>
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</tr>
<tr>
<td>Goncalves et al(^{25})</td>
<td>35/44</td>
<td>6/24</td>
<td>11.67 (3.59-37.93)</td>
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</tr>
<tr>
<td>Yost et al(^{33})</td>
<td>24/27</td>
<td>0/6</td>
<td>91.00 (4.15-1993.50)</td>
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</tr>
<tr>
<td>Skipper et al(^{31})</td>
<td>8/17</td>
<td>4/12</td>
<td>1.78 (0.38-8.23)</td>
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</tr>
<tr>
<td>Ozden and DiBiasi(^{30})</td>
<td>27/40</td>
<td>4/8</td>
<td>2.08 (0.45-9.65)</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>322</strong></td>
<td><strong>112</strong></td>
<td><strong>11.57 (3.82-35.05)</strong></td>
<td></td>
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</tbody>
</table>

**Figure 4.** Forest plot of partial relief of symptoms in patients with right upper quadrant pain without gallstones. CI indicates confidence interval; OR, odds ratio.

<table>
<thead>
<tr>
<th>Source</th>
<th>Surgical Treatment</th>
<th>Medical Treatment</th>
<th>OR (95% CI)</th>
<th>Favors surgical treatment</th>
</tr>
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<tbody>
<tr>
<td>Misra et al(^{29})</td>
<td>9/69</td>
<td>12/29</td>
<td>0.21 (0.08-0.59)</td>
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<td>Zech et al(^{24})</td>
<td>2/59</td>
<td>7/11</td>
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<td>Khosla et al(^{32})</td>
<td>8/30</td>
<td>2/5</td>
<td>0.55 (0.08-3.89)</td>
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<td>Mishkind et al(^{30})</td>
<td>11/27</td>
<td>7/15</td>
<td>0.78 (0.22-2.80)</td>
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<td>Goncalves et al(^{25})</td>
<td>9/44</td>
<td>0/24</td>
<td>13.11 (0.72-235.94)</td>
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<td>Yost et al(^{33})</td>
<td>2/27</td>
<td>4/8</td>
<td>0.94 (0.00-0.37)</td>
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<tr>
<td>Skipper et al(^{31})</td>
<td>6/17</td>
<td>8/12</td>
<td>0.27 (0.06-1.30)</td>
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<tr>
<td>Middleton and Williams(^{27})</td>
<td>134/140</td>
<td>3/41</td>
<td>282.89 (67.57-1184.42)</td>
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<tr>
<td>Ozden and DiBiasi(^{30})</td>
<td>11/40</td>
<td>3/8</td>
<td>0.63 (0.13-3.10)</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>453</strong></td>
<td><strong>151</strong></td>
<td><strong>0.70 (0.10-4.92)</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 5.** Funnel plot of higher-quality studies (Newcastle-Ottawa Scale score >6) evaluating the association between surgery and symptom relief. The diagonal lines represent the 95% confidence interval around the overall effect estimate, which is indicated by the vertical line. The effect of each study is marked by a circle and its size represents the weighting it has been assigned in the analysis. Uneven distribution of the studies around the 95% confidence interval line (inverted shaped funnel) suggests the presence of publication bias, and outliers provide definite evidence of such bias.

Duration of Follow-up

In 1 study, follow-up was limited to 3 months and another did not specify the duration of follow-up. After excluding these 2 studies (n = 534; 8 studies\(^{25,26,28-31,34}\)), surgery was still found to be beneficial in patients with any symptom relief (OR, 8.45; 95% CI, 2.64-27.06; \(I^2 = 69.7\)) (n = 390; 7 studies\(^{25,26,28-31,34}\)).

**VALIDITY ASSESSMENT**

We created funnel plots (Figure 5) using the log of the relative risk and the standard error of the log of the relative risk as x- and y-axes, respectively. Clustering of studies in a narrow band of the y-axis indicates that the studies have nearly the same precision, while clustering in the x-axis indicates that they are similar with respect to the effect size. Not all of the high-quality studies fall within the 95% CI (the inverted funnel), suggesting variability with respect to precision and effect. They were not distributed equally along the y-axis in the funnel plot, suggesting the possibility of publication bias (Figure 5). How-
ever, this was not supported by quantitative assessment of publication bias using the Egger et al \(P = .07, \text{ CI includes} \ 0\) or Begg and Mazumdar \(P = .10\) tests.

**COMMENT**

How to treat symptomatic patients without gallstones and with an abnormal HIDA scan result is a decision conundrum for physicians, because there is still uncertainty as to whether surgery is truly beneficial. These patients are often referred to surgeons, who are then faced with the decision of either continuing medical treatment or proceeding to cholecystectomy. Based on this meta-analysis of observational studies, symptomatic patients with a positive HIDA scan result and no evidence of gallstones experience superior outcomes following cholecystectomy than with medical treatment.

We did not determine whether laparoscopic cholecystectomy was superior to the open technique because laparoscopy has replaced the open approach when feasible owing to the decreased morbidity in terms of length of stay and earlier return to work. The laparoscopic approach has become the standard for asymptomatic patients with cholelithiasis. To date, there is only 1 such randomized controlled trial, which was conducted more than 16 years ago. Yap et al\(^{36}\) randomized 21 patients with an abnormal gallbladder ejection fraction to surgery or medical treatment and followed up these patients for a mean duration of 34 months. Ninety-one percent of patients undergoing cholecystectomy reported complete symptom relief.

In the general population, the prevalence of biliary type pain without gallstones is approximately 2.4%,\(^{37}\) with a preponderance in females (20.7%).\(^{38}\) In general surgical practices, nearly a third of all gallbladders are removed owing to biliary dyskinesia.\(^{39,40}\)

Patients without gallstones and inflammation of the gallbladder who are symptomatic receive diagnoses of biliary dyskinesia and/or are referred to as having chronic acalculous gallbladder disease. Cases with inflammation of the gallbladder are diagnosed with acalculous cholecystitis. The pathophysiology of biliary dyskinesia still remains largely unknown, with several theories postulated, including narrowing of the cystic or common hepatic ducts in the presence of decreased gallbladder ejection fraction.\(^{36,41}\) For gastroenterologists, biliary dyskinesia may be a synonym for sphincter of Oddi dysfunction, which is a distinct disease process.\(^{42}\) Low gallbladder ejection fraction is not specific to biliary dyskinesia and may occur in healthy asymptomatic participants,\(^{43}\) creating additional problems in defining biliary dyskinesia.

Before receiving the diagnosis of biliary dyskinesia, symptomatic patients usually undergo ultrasonography to exclude the presence of gallstones. Despite this, some individuals are subsequently found to have gallstones intraoperatively. We suggest that a clinical history compatible with biliary disease followed by ultrasonography and esophagogastroduodenoscopy to exclude alternative diagnoses be performed prior to ordering a HIDA scan. Four\(^{25,26,30,33}\) of the 11 studies did not report whether or not nondyspeptic symptoms, such as nausea and bloating, were investigated extensively and whether or not alternative diagnoses, such as irritable bowel syndrome, gastroesophageal reflux disease, or colonic inertia, were made at a later date; these would have influenced the postoperative outcome. Although the analyses in the partial symptom relief group indicated that surgery was not beneficial, we believe that this may identify a group of individuals who may need to undergo additional investigations to establish a definitive cause of their symptoms.

Most of the studies that were excluded from this meta-analysis were excluded primarily because they had only 1 study arm that was composed only of patients undergoing cholecystectomy, making it impossible to make valid comparisons. Further compounding the problem, these studies were typically retrospective with relatively small sample sizes and more than likely to be underpowered.

The technetium Tc 99m HIDA scan evaluates gallbladder contractility using a CCK infusion. An abnormal result is a gallbladder ejection fraction of 40% or less as defined by the Rome II Consensus.\(^6\) The cut-off value was derived from a group of healthy volunteers. Studies from the United States have tended to use less than 35% as the cut-off value, which was used by Krishnamurthy et al\(^{49,50}\) in the 1980s, while others have used values ranging from 40% to 65%.\(^{32,34,41,46,47}\) The technique used to derive this value is of interest in this meta-analysis, as it may account for some of the significant heterogeneity observed among the studies. Traditionally, CCK is given as a bolus infusion for 3 minutes, which is followed by imaging with a gamma camera, but some clinicians\(^{2,33,46}\) administered CCK continuously throughout the assessment (30-60 minutes), because it is believed that this achieves a more consistent result, as it is more physiologic. The slow infusion rate results in an overall increase in mean gallbladder ejection fraction compared with the rapid infusion rate. The slower rate has less intersubject and intrasubject variability and permits the calculation of a meaningful cut-off value for gallbladder ejection fraction in healthy individuals.\(^49\) We assessed whether the duration of CCK infusion may have explained some of the heterogeneity observed in this study. The sensitivity analyses suggest that studies that used an infusion of less than 3 minutes lack heterogeneity.

Increasingly, it has been recognized that the gallbladder may not be responsible for a decreased gallbladder ejection fraction, because outflow obstruction from abnormalities of the cystic duct or sphincter of Oddi may also result in delayed gallbladder emptying.\(^42,50\) Other causes of a reduced gallbladder ejection fraction include use of opiates\(^{31}\) and calcium channel blockers.\(^{32}\) The lack of consensus on the duration and dose of CCK may be a considerable source of heterogeneity. Sensitivity analysis was therefore performed to assess whether this affected the overall study outcome.

The authors of this article hypothesized that follow-up in a clinic would provide a more detailed evaluation of a patient’s symptoms compared with telephonic or questionnaire-based interviews. Sensitivity analyses could not be conducted, because only 1 study\(^{33,41}\) followed up patients exclusively in clinics and 2 studies\(^{31,33}\) used a combination of clinic and telephonic in-
tervies but did not report individual results based on follow-up. We believe that the small number of participants in these studies would not have provided a meaningful result, therefore limiting interpretation. In addition, the variation in methods of follow-up may have contributed to significant heterogeneity.

Symptomatic patients without evidence of gallstones and with a negative HIDA scan result do benefit from surgery (57%-100% symptomatic relief). However, nonoperative intervention in this group of patients leads to a better relief rate without surgery (70%-84%).

Some studies have indicated that histologic findings predict clinical outcomes in patients with biliary dyskinesia. However, not all patients who experience symptom relief following surgery for presumed biliary dyskinesia have abnormal gallbladder pathology. We could not conduct a sensitivity analysis based on histopathologic findings, though several studies reported pathologic findings in patients undergoing cholecystectomy. We could not discern the individual pathologic diagnosis of each patient and therefore could not correlate outcomes to histology. Pathologic diagnosis in predicting which patients would benefit from surgery in the presence of clinical symptoms has little value, because histological diagnosis is necessarily a postoperative finding.

With inclusion of observational studies in this meta-analysis, there is a possibility of selection bias. There was no masking of either the patients or physicians. This created the possibility of bias for patients, especially in the surgical arm, if they were expecting a better outcome after surgery compared with patients in the medical arm.

The paucity of information on patient characteristics in the eligible studies meant that we could not conduct sensitivity analyses based on age, sex, or race/ethnicity. Also, clinical information on the patients who were treated medically was not available in the studies. This information could be very pertinent, as those who had undergone endoscopic sphincterotomies may have reported symptom improvement, which may have reduced the perceived benefit of surgical intervention.

The possibility of selection bias introduced into the original studies because patients were not prospectively selected is noted. The presence of publication bias is evident on visual inspection of the funnel plot owing to its asymmetrical inverted funnel distribution (Figure 5). However, quantitative assessment of publication bias using the Egger et al and the Begg and Mazumdar tests did not confirm this. Use of such quantitative tests for this purpose may not resolve this issue, as conflicting results have been reported from the same study using both methods. Differences between study populations have resulted in heterogeneity in some of the analyses. Several of the sensitivity analyses are constrained by the limited number of studies, small sample sizes, and wide standard deviations, which in turn limit confidence in drawing conclusions, as reflected by the wide CIs. Ideal studies for a meta-analysis is high-quality, large, randomized trials. Without these, we have to make the best of the currently available information, as is the case here. This is the justification for including, for example, the study by Watson et al, which met our predefined inclusion criteria. Despite these limitations, our conclusions remain fundamentally the same, with more than 96% of participants (n=462) reporting some degree of symptom relief following surgery and only 45% reporting similar symptom relief with medical treatment (n=153). The beneficial effects of surgery in symptomatic patients with positive HIDA scan results seem apparent.

CONCLUSIONS

There is wide variability in data reporting in studies of patients with positive HIDA scan results and no gallstones, particularly with respect to symptom relief and duration of follow-up. This may account for the significant heterogeneity observed in sensitivity analyses. In symptomatic patients without gallstones, a HIDA scan with a low ejection fraction is a legitimate indicator for cholecystectomy and likely a predictor of favorable postoperative outcomes.

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