Hepatobiliary phase of gadoxetic acid-enhanced MR in patients suspected of having gallbladder dyskinesia: comparison with hepatobiliary scintigraphy

Jeong Kyong Lee *, Yookyung Kim, Sangmin Lee, Ji Eun Park

Department of Radiology, School of Medicine, Ewha Womans University, 911-1 Mokdong, Yangcheon-gu, Seoul, 158-710, Korea

Abstract

Objective: To compare hepatobiliary phase of gadoxetic acid-enhanced magnetic resonance (HMR) and hepatobiliary scintigraphy (HBS) for evaluation of cystic duct patency and gallbladder contractility in patients suspected of having gallbladder dyskinesia.

Materials and methods: Eighteen patients underwent HMR and HBS. Cystic duct patency and gallbladder ejection fraction (GBEF) were compared to determine a significant difference between HMR and HBS.

Results: HMR and HBS had 15 concordant and 3 discordant results for cystic duct patency. GBEF in eight patients showed no significant difference between both modalities.

Conclusion: HMR may be an alternative to HBS for the functional evaluation of cystic duct patency and GBEF.

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1. Introduction

Hepatobiliary scintigraphy (HBS) has been an unchallenged modality for the functional evaluation of the gallbladder. In the clinical evaluation of a patient presenting with right upper quadrant tenderness and equivocal imaging findings for acute cholecystitis, HBS has played an important role by demonstrating the functional evaluation of cystic duct patency and gallbladder contractility [1,2]. The functional information of gallbladder is useful for the diagnosis of acute cholecystitis and other functional gallbladder diseases such as gallbladder dyskinesia that frequently manifests as biliary colic mimicking acute cholecystitis and has traditionally been evaluated by assessment of gallbladder contractility based on the ejection fraction [3–5]. Magnetic resonance (MR) cholangiography using mangafodipir trisodium for the evaluation of cystic duct patency and gallbladder contractility measurement by ultrasound (US) have been reported [5,6] however not widely accepted. Recently, commercial availability of hepatobiliary specific gadolinium-based MR contrast agent has been increasing, and MR using a gadolinium agent with a higher rate of hepatobiliary excretion has shown promise as an alternative to HBS for the functional evaluation of gallbladder [7–9]. MR including the hepatobiliary phase may be able to provide functional and morphological information on the gallbladder simultaneously. In this study, we prospectively compared the hepatobiliary phase of gadoxetic acid-enhanced MR with HBS for the evaluation of cystic duct patency and gallbladder contractility in patients suspected of having gallbladder dyskinesia.

2. Materials and methods

2.1. Patients

This study was approved by our institutional review board, and written informed consent was obtained from all participants prior to entering the study. Between April 2008 and December 2010, 18 consecutive patients (8 men and 10 women; age range, 16–83 years; mean age, 50.6 years) were enrolled in this study prospectively. The inclusion criteria were as follows: (a) Patients that had a sudden onset of right upper quadrant tenderness, (b) patients that showed equivocal findings for acute cholecystitis by computed tomography (CT) and/or US obtained at the time of pain onset (i.e., the absence of gallstone, gallbladder wall thickening greater than 4 mm, pericholecystic inflammation, and fluid collection, but with the presence of the sonographic Murphy sign or gallbladder distention greater than 5 cm) and suspected of having the possibility of gallbladder dyskinesia, (c) patients who did not have cystic and bile duct dilatation (greater than 8 mm) or obstruction by a stone or mass at US and CT, (d) CT that showed no evidence of disease that causes tenderness in other organs, and (e) patients who underwent gadoxetic acid-enhanced MR imaging and HBS on the same day. All patients underwent MR imaging and HBS after CT and/or US. The mean interval between CT or US and MR imaging was 21.9 h (range, 0–60 h). MR imaging was performed except poststimulant
images. Then, HBS was completed including poststimulant images. Poststimulant hepatobiliary phase MR images were acquired immediately after the completion of HBS. A flow chart for the process of imaging was presented in Fig. 1. Patients were treated either by a cholecystectomy ($n=11$) or by conservative treatment without antibiotics ($n=7$) based on the clinical decision. All patients showed the resolution of the tenderness following treatment and underwent a clinical with or without radiologic follow-up.

2.2. Imaging

US scan was performed by two radiologists (J.K.L. and S.L.) using high-resolution US (HDI 5000; Philips Medical Systems, Bothell, WA) and 2- to 5-MHz convex transducer in all patients.

CT examinations were performed by using 64-detector-row scanners (Sensation; Siemens Medical Solutions, Erlangen, Germany) in all patients with collimation of 0.67 mm, pitch of 1, reconstruction interval of 5 mm, 120 kVp, $90^\circ$–$140$ mAs. Precontrast scan was acquired at the level of liver. One hundred and twenty milliliters of contrast media was injected intravenously at a rate of 3 ml/s by using an automatic power injector, and venous phase images involving the diaphragm to perineum were scanned 100 s after injection.

MR imaging was performed by using a 3.0-T system (Achieva; Philips Medical Systems) in all patients with phased-array coils. All images were obtained after 6–8 h fast with breath holds. Table 1 provides a summary of the pulse sequence parameters used. For contrast-enhanced MR imaging, 0.025 mmol/kg of body weighted of gadoxetic acid disodium (Primovist; Bayer-Schering, Berlin, Germany) was injected as a rapid bolus and was immediately followed by a saline flush of 15–20 ml. Hepatobiliary phase was obtained at 20 and 30 min after the injection of the intravenous contrast agent using a three-dimensional T1-weighted gradient-echo sequence. Additional hepatobiliary phase was acquired 45–60 min after a fatty-meal ingestion as a stimulant for gallbladder contraction when a patient was possible to eat the fatty meal. Whole milk (250 ml) and two eggs were used as the fatty meal.

HBS was performed after intravenous administration of 5 mCi of technetium 99m-tagged diisopropyl-iminodiacetic acid (IDA). Serial 15-min-long imaging in the anterior projection was performed at 5, 30, 60, and 90 min with a standard camera with a large field of view and a high-resolution collimator. Additional lateral and left anterior oblique images were obtained 1 h after injection and an anterior image was obtained at 45–60 min after indigestion of a fatty meal. If gallbladder activity was not visualized, the study was then continued every hour up to 4 h after injection of IDA.

2.3. Image analysis

Two authors (J.K.L. and S.L.) with 9 and 2 years of experience in abdominal radiology prospectively reviewed the gadoxetic acid-enhanced MR and HBS results in consensus. T1- and T2-weighted MR images were evaluated for the presence of obstruction at the cystic or common ducts. The hepatobiliary phase of the MR images was evaluated for the presence of contrast material in gallbladder at 20 min, 30 min, and poststimulant images. Gallbladder ejection fraction (GBEF) was calculated on MR as follows: GBEF (%)=$100 \times (GBV_{30}−GBV_{fm})/GBV_{30}$. GBV$_{30}$ and GBV$_{fm}$ are the gallbladder volumes at the 30 min and poststimulant images, respectively. Gallbladder volume was measured by drawing the gallbladder area at the MR axial images using the manual method on PACS and adding the areas. HBS was evaluated for the time of gallbladder visualization. GBEF was calculated on HBS using the maximum counts minus counts at 45–60 min after a fatty-meal ingestion divided by the maximum counts. The reflux of contrast and radiotracer into the gallbladder at the hepatobiliary phase of gadoxetic acid-enhanced MR and HBS were correlated with each other and with the clinical results. Lastly, the coincidence of GBEF measured at gadoxetic acid-enhanced MR and HBS was evaluated.

2.4. Statistical analysis

Comparison between the hepatobiliary phase of gadoxetic acid-enhanced MR and HBS in the diagnosis of cystic duct patency and the measurement of GBEF was performed by the McNemar test and Wilcoxon signed ranks test, respectively, and $P<.05$ was considered to

Table 1

A summary of MR pulse sequence parameters

<table>
<thead>
<tr>
<th></th>
<th>Fat-suppressed single-shot</th>
<th>FSE T2-weighted sequence</th>
<th>3D T1-weighted GE sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plane</td>
<td>Axial, coronal</td>
<td>Axial</td>
<td>Axial</td>
</tr>
<tr>
<td>Repetition time (ms)</td>
<td>1710</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Echo time (ms)</td>
<td>80</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Flip angle (°)</td>
<td>–</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Section thickness (mm)</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Intersection gap (mm)</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Matrix</td>
<td>220×216</td>
<td>228×228</td>
<td>228×228</td>
</tr>
</tbody>
</table>

Abbreviations used: FSE, fast spin-echo; 3D, three-dimensional; GE, gradient-echo.
indicate a statistically significant difference. SPSS software (SPSS, version 17.0; SPSS, Chicago, IL) was used for the statistical analysis.

3. Results

3.1. Diagnostic performance of MR and HBS

All patients showed biliary and duodenal excretion at the hepatobiliary phase of gadoxetic acid-enhanced MR and did not show cystic or common duct obstruction at T2-weighted MR. In total, 15 patients demonstrated concordant results at the hepatobiliary phase MR and HBS (Table 2). Of these, five showed no reflux of contrast and radiotracer into the gallbladder at the hepatobiliary phase MR and HBS, respectively. Two of the five improved by conservative treatment. Three patients underwent a cholecystectomy and were found to have acute cholecystitis (Fig. 2). One of the three patients had several tiny stones on the pathologic examination. Reflux of contrast and radiotracer into the gallbladder was present at both imaging modalities in 10 patients. Delayed reflux of contrast and radiotracer into the gallbladder was identified in 2 of the 10 patients at 90–120 min hepatobiliary phase MR obtained after the indigestion of the fatty meal and at 90 min HBS. Six of the ten patients underwent a cholecystectomy and were found to have chronic inflammation. The four remaining patients improved by conservative treatment. Discordant results were demonstrated in three patients between both imaging modalities. In two patients, reflux of contrast into the gallbladder was present at the 30 min hepatobiliary phase MR image and poststimulant images (Fig. 3). However, the gallbladder was not visualized at HBS. Both patients underwent a cholecystectomy and were confirmed to have chronic inflammation. In one patient showing a discordant result, reflux of contrast was not present at the hepatobiliary phase MR and radiotracer was present at HBS. The patient improved by conservative treatment. In 11 patients that underwent surgery, the mean interval between surgery and imaging was 2.2 days and ranged from 0 to 5 days. The hepatobiliary phase MR and HBS were not statistically different in the diagnosis of cystic duct patency ($P=1.0$).

3.2. Diagnosis of gallbladder dyskinesia by ejection fraction

GBEF was calculated in 14 of 18 patients at the hepatobiliary phase MR and in nine patients at HBS (Table 3). In four patients, the hepatobiliary phase MR could not be performed after a fatty meal. Of these four patients, three had to keep fasting because of a scheduled cholecystectomy on the same day and one would not cooperate to undergo more delayed phase MR imaging. In nine patients, HBS was not performed after a fatty meal, since the gallbladder was not visualized in seven patients and two patients had to keep fasting due to a scheduled operation. GBEF was available at both imaging modalities in eight patients. GBEF did not show a significant difference at both imaging modalities ($P=.068$). The calculated GBEF was smaller at the hepatobiliary phase MR than HBS in six patients. Two patients were diagnosed as gallbladder dyskinesia with a GBEF less than 40% for both imaging modalities (Fig. 4). One of the two patients improved by a cholecystectomy and was diagnosed with chronic inflammation on pathologic examination. The other patient improved by conservative treatment. One patient showed a GBEF less than 40% at the hepatobiliary phase MR alone and a GBEF of 79% at HBS. This patient improved by conservative treatment. GBEF could be calculated at the hepatobiliary phase MR alone in six patients, since the gallbladder was not visualized at HBS. Two of the six patients had acute cholecystitis on pathologic examination and a reversed GBEF of $−6.3\%$ and $−18\%$, which corresponded with an increase in gallbladder volume after a fatty meal. Three patients showed severely decreased contractility (GBEF= $−2.6\%$ to $34\%$). Of the three patients, two improved by cholecystectomy, revealing chronic inflammation. The remaining patient showed a GBEF of 45.8% and improved by conservative treatment. One patient who did not undergo a hepatobiliary

Table 2

<table>
<thead>
<tr>
<th>Results</th>
<th>MR</th>
<th>HBS</th>
<th>Patients Outcome</th>
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<tbody>
<tr>
<td>Concordant (n=10)</td>
<td>Reflux of contrast into gallbladder</td>
<td>Visualization of gallbladder</td>
<td>Cholecystectomy; chronic inflammation (n=6) Improved by conservative treatment (n=4)</td>
</tr>
<tr>
<td>Concordant (n=5)</td>
<td>No reflux of contrast into gallbladder</td>
<td>Nonvisualization</td>
<td>Cholecystectomy; acute cholecystitis (n=3) Improved by conservative treatment (n=2)</td>
</tr>
<tr>
<td>Discordant (n=2)</td>
<td>Reflux of contrast into gallbladder</td>
<td>Nonvisualization</td>
<td>Cholecystectomy; chronic inflammation (n=2)</td>
</tr>
<tr>
<td>Discordant (n=1)</td>
<td>No reflux of contrast into gallbladder</td>
<td>Visualization</td>
<td>Improved by conservative treatment (n=1)</td>
</tr>
</tbody>
</table>

Note: n is the number of patients.
phase MR image after a fatty meal showed a GBEF of 49% at HBS and improved by conservative treatment.

4. Discussion

Gallbladder dyskinesia refers to the clinical entity of right upper quadrant symptoms of biliary colic and abnormal GBEF in the absence of gallstones or sludge [3]. Terminology can be confusing and numerous other names have been used for this entity (i.e., chronic acalculous cholecystitis, cystic duct syndrome, functional gallbladder disease, and so on) [10]. The functional biliary pain is most often attributed to abnormal gallbladder motility [4]. The diagnosis and treatment of gallbladder dyskinesia remains controversial and has been based on the information of gallbladder contractility at cholecystokinin HBS. Patients are diagnosed with gallbladder dyskinesia when GBEF is less than 35–50% and may benefit from surgery when GBEF is less than 40% [4,11–14]. In this

Table 3

Results of GBEF by MR and HBS

<table>
<thead>
<tr>
<th>Gallbladder contractility</th>
<th>GBEF (%) by MR</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>≥60</td>
</tr>
<tr>
<td>GBEF (%) by HBS</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>OP (n=2); CC</td>
</tr>
<tr>
<td>50 ≤ EF &lt; 60</td>
<td>CT (n=1)</td>
</tr>
<tr>
<td>40 ≤ EF &lt; 50</td>
<td>OP (n=1); CC</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>CT (n=1)</td>
</tr>
<tr>
<td>Nonvisualization of gallbladder</td>
<td>CT (n=1)</td>
</tr>
</tbody>
</table>

Abbreviations used: OP, cholecystectomy; CT, improved by conservative treatment; AC, acute cholecystitis on pathologic examination; CC, chronic inflammation on pathologic examination; NA, nonapplicable; n, number of patients.

* Patients showed no contrast reflux into gallbladder at the hepatobiliary phase of gadoxetic acid-enhanced MR.

* Patients showed contrast reflux into gallbladder at the hepatobiliary phase of gadoxetic acid-enhanced MR.
study, gallbladder dyskinesia was diagnosed in patients with GBEF less than 40%. On pathologic examination of gallbladder dyskinesia, there is histologic evidence for chronic cholecystitis [1].

The functional information is important for the clinical evaluation of the patient presenting with right upper quadrant tenderness in the absence of specific radiologic findings for acute cholecystitis, since gallbladder dyskinesia can be part of the differential diagnoses of the patients. When the diagnosis of acute cholecystitis is equivocal on US or CT, HBS that can visualize the bile flow through the cystic duct directly and as a result has been considered as the most accurate test for acute cholecystitis with a sensitivity of 97% and a specificity of 87% [1].

Although HBS has been regarded as the most accurate study for cholecystitis, it is usually reserved for clinical situations in which there is diagnostic ambiguity at other imaging study types such as US, since HBS has a high false-positive rate and a lack of information on the gallstone or gallbladder wall [1,2]. Gadobenate dimeglumine is the contrast agent that combines the imaging properties of extracellular agents during the arterial and portal venous phases with the imaging properties of hepatobiliary agents in the delayed phase. The increased hepatic excretion of gadobenate dimeglumine (50%) allows for the functional assessment of the biliary system within 20 min after administration in patients with normal hepatic function [7,15]. In this study, we tried to demonstrate that the hepatobiliary phase of gadobenate dimeglumine-enhanced MR could be the most useful modality for gallbladder disease by providing functional information including the patency of the cystic duct and gallbladder contractility as well as morphologic information and, therefore, could be a substitute for HBS. Krishnan et al. reported that reflux of contrast into the gallbladder was observed within 25 min after the contrast administration in 92% (120/130) of patients [7]. For the most part, we could decide the patency of cystic duct at the hepatobiliary phase MR and HBS at 30 min. Two patients showed delayed reflux at 90 min HBS and 90–120 min hepatobiliary phase MR and were diagnosed as having a patent cystic duct, since nonvisualization of the gallbladder is determined with higher specificity if HBS at 3–4 h shows no gallbladder visualization [10,16]. We used a fatty meal as a stimulant for gallbladder contraction, although exogenous cholecystokinin is widely used to induce a gallbladder contraction. Controversy exists on using a fatty meal as a chologogue stimulant in HBS, since a fatty meal has potential disadvantages over cholecystokinin, in that GBEF measurement is time dependant, gallbladder emptying has to be monitored for a minimum of 60 min after test meal ingestion, and fatty meal is poorly standardized [17–19]. However, a fatty meal is more physiologic and less expensive [18]. A recent report demonstrated that a GBEF measurement obtained by fatty-meal HBS was not affected by further extension of GBEF acquisition beyond the 45–60 min acquisition time [17]. In our country, cholecystokinin is not commonly used; hence, a fatty-meal HBS is usually used to evoke a gallbladder contraction. To minimize any biases, we measured GBEF by both imaging modalities at the same time and in the same patients.

The results from the hepatobiliary phase MR regarding the presence of cystic duct patency and GBEF agreed well with those from HBS in the study. Both imaging modalities diagnosed three acute cholecystitis correctly by cystic duct obstruction. HBS showed one more false-positive case (i.e., nonvisualization of gallbladder or no reflux of contrast into gallbladder without acute cholecystitis) than the hepatobiliary phase MR, and false-positive cases usually result in the consideration of a cholecystectomy or unnecessary antibiotic treatment. The false-positive rate of HBS was reported as 10–20%, and largely explained by fasting longer than 24 h, insufficient resistance at the sphincter of Oddi, or cystic duct obstruction induced by chronic inflammation [2]. Two patients showed false-positive results for both modalities, and for these patients, the GBEF was only available for the MR modality and measured — 2.6% and 45.8%, respectively. The decrease of gallbladder volume at the hepatobiliary MR after a fatty meal may mean that the patency of the cystic duct and may be helpful for reducing false-positive results. Two patients with their gallbladders not filled at HBS alone were available on measurement of GBEF at the hepatobiliary phase MR and the GBEF was less than 40%. Those patients were found to have chronic cholecystitis at surgery and could be verified as gallbladder dyskinesia. The hepatobiliary phase MR could provide GBEF even when the gallbladder was not visualized at HBS. The GBEF measured less at the hepatobiliary phase MR than HBS in six of eight patients. This is likely due to the discrepancy between detecting the difference of the radioactivity counts at HBS and the spatial change of the gallbladder wall at MR [5]. Since the hepatobiliary phase of MR at 30 min was performed before starting HBS, patients had fasted longer at that time of obtaining a HBS. Therefore, the gallbladder volume acquired before a fatty meal might be larger in HBS than the hepatobiliary phase MR, which could result in the smaller GBEF at the hepatobiliary phase MR.

There are several limitations to this study. First, only a small number of patients were included in this preliminary study and the statistical power can be limited. Second, not all patients underwent surgery. Some patients were given a final diagnosis based on clinical features and underwent relatively short term clinical follow-up. Patients with acute cholecystitis would have worse symptoms and laboratory results within several hours to days by conservative treatment and eventually undergo surgery. Therefore, we verified patients who improved by conservative treatment as not having acute cholecystitis. Third, the final diagnosis of gallbladder dyskinesia does not seem to be straightforward since the diagnosis is based on decreased GBEF and the exclusion of diseases in other organs causing the same symptoms, and there is no unique surgical or pathologic finding. Lastly, GBEF measured at HBS or MR would be the reference standard.

In summary, the hepatobiliary phase of gadobenate dimeglumine-enhanced MR correlated well with HBS in the diagnosis of the cystic duct patency in patients who had equivocal findings for acute cholecystitis at US and CT. There was no significant difference in GBEF measured at both imaging modalities. The hepatobiliary phase MR could provide GBEF as a diagnostic criterion for gallbladder dyskinesia, even in patients whose gallbladder was not visualized at HBS.

In conclusion, the hepatobiliary phase of gadobenate dimeglumine-enhanced MR is a potential alternative to HBS for the functional evaluation of cystic duct patency and GBEF. Gadobenate dimeglumine-enhanced MR has an advantage in demonstrating the morphological and functional abnormality of the gallbladder.

Acknowledgments

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References

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