Improving Hepatobiliary Imaging as a Physiologic Test with Superior Clinical Outcomes

ABSTRACT
This study aims at prospectively evaluating the difference in the effect of cholecystokinin (CCK) and half-and-half milk (HHM) administered in the same patient on gallbladder contractility and correlation with clinical outcomes. Upon gallbladder visualization during standard hepatobiliary imaging, 0.02 µg/kg of CCK was injected over 3 min, and additional 30 min of dynamic imaging was obtained. Patients with gallbladder ejection fraction (GBEF) <35% after CCK were administered 8 oz of HHM followed by 30 min of imaging. The GBEF was recalculated. The number of patients whom GBEF changed from below 35% (abnormal) after CCK to above 35% (normal) after HHM was recorded. Follow-up of the clinical outcome at 6 months was performed. Fifty patients with abnormal GBEF were prospectively included. The average GBEF after CCK was 14.7% ± 8.5% and after HHM was 30.7% ± 20.8%. The average increase in GBEF with HHM was 16.0% ± 22.2%. The GBEF changed from abnormal to normal in 17 patients (34%). The remaining 33 patients remained abnormal. Clinical outcomes at 6 months were available in 47 patients. Cholecystectomy was performed in 60% of patients with abnormal GBEF with CCK and HHM with resolution or improvement of pain. Two of 16 patients (12%) with abnormal GBEF after CCK but normal after HHM had cholecystectomies with pain improvement, while 8 out of these patients (50%) were diagnosed and treated with other disorders and improved. Hepatobiliary imaging with HHM stimulation is a superior physiologic test which can lower the number of unnecessary cholecystectomies and misdiagnoses as functional cholecystitis.

Keywords: Cholecystokinin, cholescintigraphy, fatty meal, gallbladder ejection fraction, hepatobiliary imaging, milk

INTRODUCTION
Hepatobiliary imaging plays an important role in the evaluation and management of many patients with gastrointestinal symptoms and abdominal pain. It is estimated that approximately 30,000–90,000 patients/year undergo cholecystectomy with the diagnosis of acalculous cholecystitis. The ease of performing laparoscopic cholecystectomy might have inflated the true incidence of this diagnosis. It has also been reported that cholecystectomies have only 50%–75% success rate in eliminating the symptoms. Epidemiological studies found that cholecystectomies for functional cholecystitis are 4–80 times more common in the United States than in Norway, Sweden, Poland, and Australia. This raises the question that many of these cholecystectomies might be unnecessary.

Since the first description of the possible accurate evaluation of gallbladder contractility using a phantom and small number of patients after cholecystokinin (CCK) administration by Krishnamurthy et al. in 1981, this test...
has gained wide acceptance as the routine standard test for evaluating gallbladder contractility. Subsequent studies and Cochrane review\(^6\) have established the cutoff value for abnormal gallbladder ejection fraction (GBEF) of <35% as abnormal and indicates decreased gallbladder contractility. Different methods of administration of CCK have been proposed as the acceptable mean to produce reliable results for the evaluation of gallbladder contractility. These include slow infusion of CCK over 30 or 60 min to mimic the physiologic excretion of CCK in the body in response to eating\(^7,8\) versus the short intravenous infusion over 3 min.\(^9\)

Fatty meals are increasingly utilized to evaluate gallbladder contractility, with the increasing shortage of CCK in the United States. The examples of acceptable fatty meals include fatty drinks, for example, Ensure or Pediasure or an in-house prepared fatty meal.\(^10\)\(^11\)\(^12\) We also noticed in one patient who underwent a hepatobiliary scan with CCK and had an abnormal GBEF <35% had returned in few months for a repeat hepatobiliary scan ordered by a different physician, with no interval intervention for his continued abdominal pain, during a time of shortage of CCK. We repeated the scan with half-and-half milk (HHM) instead of CCK, and surprisingly, the GBEF calculation was normal in the same patient. Previous studies have been conducted using regular milk with well-established gallbladder emptying response times and time-activity curves in normal men and women have been published.\(^13\) Thus, we decided to conduct a prospective study to compare GBEF in the same patients after CCK administration and HHM ingestion.

In this study, we compared the effect of CCK and HHM administered in the same patient on gallbladder contractility with follow-up on clinical outcomes of the patients.

**METHODS**

After obtained approval of this study protocol from the University of Texas-McGovern Medical School’s Institutional Review Board, we prospectively and consecutively included patients that meet the inclusion criteria into the study. This study included 50 patients who underwent hepatobiliary scan using 5–6 mCi of Tc-99m mebrofenin with CCK administration and demonstrated a reduced GBEF of <35%. CCK was administered at the end of 1 h of continuous dynamic imaging at a dose of 0.02 µg/kg as a slow intravenous injection over 3 min. After consenting to be included in the study which was performed in approximately 10–15 min, these patients were administered 8 ounces of cold HHM (Oak Farms) which contained 28 g of fat. A waiting period of 10 min after the ingestion of the milk was followed by repeat of 30 min dynamic imaging of the upper abdomen at 1 min/frame rate. The GBEF was recalculated using the same computer analysis program used for calculating the GBEF after CCK stimulation.

Data were collected, including the patients’ demographics, clinical symptoms, findings from other imaging modalities, pain medications, and the GBEF with CCK and HHM stimulation. In addition, data regarding the reproduction of pain during CCK or HHM administration were obtained. The patients were contacted at 6 months to follow-up on their symptoms, particularly abdominal pain, any procedures, or change of medications. The abdominal pain was evaluated using a pain scale from 0 to 10 for all patients before the hepatobiliary scan and at 6 months follow-up.

**Statistical analysis**

Distributions of continuous variables were verified to be normal using the Kolmogorov–Smirnov test. Continuous variables were summarized as mean and standard deviation. Increase in GBEF was evaluated by the paired t-test. We reported two-sided P values, and P < 0.05 was considered as statistically significant.

**RESULTS**

A total of 50 patients were prospectively included in our study, 19 males and 31 females, with a mean age of 48.6 ± 14.7 years. Nineteen of these patients were Caucasian, 13 African American, 4 Asian, and 14 others. All patients had an abnormal GBEF after CCK with an average of 14.7% ± 8.5% (range 0%–33%). The recalculated average GBEF after HHM administration was 30.7% ± 20.8% (range 0%–88%). The average increase in GBEF of all the patients with the administration of HHM after CCK was 16.0% ± 22.2% (range 0%–88%). The increase in GBEF after HHM was statistically significant with P < 0.001.

The GBEF changed from abnormal (GBEF <35%) to normal (GBEF >35%) in 17 out of the 50 patients (34%), with an average increase in their GBEF of 39.2% ± 18.5% (P < 0.01). Examples of patients with a significant change of GBEF with HHM are demonstrated in Figures 1 and 2. The remaining 33 patients had an increase in their GBEF at an average 4.1% ± 12.4% (P = 0.07) but remained abnormal [Figure 3]. We have also observed a more physiologic response with a gradual smooth continued drop in the time-activity curves after HHM stimulation than with CCK stimulation [Figure 4].
Only one patient had pain after CCK administration and was one of those who changed their GBEF from abnormal to normal after drinking milk. Another patient had abdominal pain after milk ingestion, and her GBEF remained abnormal with both CCK and HHM.

Clinical outcome was available in 47 patients, and 3 patients were lost to follow-up. The follow-up interval was 6 months in 45 patients and 6–12 months in 2 patients. The outcome of the two groups of patients, those with no change in their GBEF after HHM and those with normalized GBEF after HHM ingestion is summarized in Table 1.

When focusing on the group of patients with abnormal GBEF after CCK but normal after HHM (17 patients; 34%), 2 underwent cholecystectomy with improvement of their pain.
that may represent the rate of false-negative rate (12%) if HHM is to be used as the standard stimulus for hepatobiliary imaging. On the other hand, 8 patients (50%) were appropriately diagnosed with other disorders and were pain free after the treatment for these disorders but would have been considered as false positives if CCK was to be used as the only stimulus for gallbladder contractility. These eight patients were appropriately treated for H-Pylori gastritis (1 patient), kidney stones (1 patient), inflammatory bowel disease (1 patient), gastroesophageal reflux disease/gastritis (GERD) (2 patients), pancreatitis (1 patient), hyperparathyroidism (1 patient), and fatty liver (1 patient). Thus, the sensitivity, specificity, and positive predictive and negative predictive values of HHM-simulated hepatobiliary imaging are 92.6%, 57.1%, 80.6%, and 80.0%, respectively. Five patients did not improve despite a different diagnosis and treatment than chronic cholecystitis.

Figure 3: Unchanged abnormal gallbladder ejection fraction in a patient after cholecystokinin stimulation (a) calculated as 12% and after half and half milk stimulation (b) calculated as 4%

Figure 4: Comparison of the time-activity curve and gallbladder contractility in the same patient after cholecystokinin (a) showing a brief mild contraction followed by relaxation when the cholecystokinin effect fades versus after half-and-half milk (b) showing smooth gradual increasing gallbladder contraction
Thus, HHM was administered after almost 18–20 min. Limitation of our study that HHM has also, since it is found in only 5%–15% of over 600,000 cholecystectomies performed every year in the US. This points out the magnitude of possible unnecessary cholecystectomies performed based on this diagnosis. To date, the only available test to make this diagnosis is hepatobiliary scintigraphy with CCK stimulation. Hence, clearly, there are many false-positive results when CCK is used as a stimulus with hepatobiliary scan. In another large study by Eckenrode et al., cholecystectomies were performed based on patients’ symptoms rather than their hepatobiliary scan results, and they recorded the resolution of pain in 66% of patients with positive hepatobiliary scans and 77% of patients with negative hepatobiliary scans in patients with typical biliary colic symptoms versus 64% of patients with positive hepatobiliary scans and 43% of patients with negative hepatobiliary scans in patients with atypical symptoms. CCK was used as a stimulus in their study during hepatobiliary scans and they suggested that hepatobiliary scans are over-utilized in the management of patients with biliary dysfunction.

Another study by Goussous et al. compared the reproduction of pain between the two groups of patients who underwent hepatobiliary scans, one stimulated with CCK and another stimulated with fatty meal in form of one can of Ensure Plus. They found no difference in the average GBEF between the two groups, but there was a higher reproduction of pain in the group stimulated with CCK (61%) versus fatty meal (30%), which they conclude is an important predictor of good response to cholecystectomy. Morris-Stiff et al. has also reported in a large study that the reproduction of pain during stimulated hepatobiliary scan is superior to GBEF in predicting the resolution of symptoms after cholecystectomy. In our study, only one patient had pain after CCK stimulation and his GBEF actually normalized after stimulating gallbladder contractility with HHM, suggesting that the pain is likely a side effect of CCK stimulation rather than a true indication of gallbladder motility dysfunction. Furthermore, only one patient in our study had pain after HHM stimulation and her GBEF remained abnormal. Interestingly, the number of patients who experienced pain both after CCK and after HHM stimulation in our study are very low, suggesting that pain cannot be used as an indication for cholecystectomy or a predictor for relief after cholecystectomy.

The diagnosis of chronic acalculous cholecystitis has been previously questioned by Lillemoe since it is found in only 5%–15% of those with abnormal gallbladder ejection fraction after cholecystokinin but normal with half and half milk.
their gallbladder from any sludge knowing that 30 min is long enough interval to prevent any interference of CCK premedication with the accuracy of the hepatobiliary scan.

Most importantly, all the patients enjoyed the cold HHM and had no difficulty of drinking the whole glass of 8 oz, especially after fasting for the test.

CONCLUSION

In conclusion, our study demonstrated that HHM is a superior and more accurate stimulus for gallbladder contractility and calculation of GBEF. It also suggests better outcomes for the management of gallbladder dysfunction, although our results did not reach statistical significance. However, the difference between the mean GBEF after HHM was significantly higher than with CCK with \( P < 0.001 \).

Thus, we recommend the use of HHM as the standard stimulus for HIDA scans to diagnose gallbladder motility dysfunction. This will also eliminate the difficulties in performing hepatobiliary scans in the face of CCK frequent shortages in the US.

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Conflicts of interest
There are no conflicts of interest.

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