Original Article

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.[1] 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.[2,3] 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.[4] 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,[5] this test

Isis W. Gayed, Lydia Dawood, Zhang Xu[1], Grace Rizk, Andrew Dupont[2], Monica Atta, Emily K. Robinson[3]

Departments of Diagnostic and Interventional Imaging, Nuclear Medicine Section, Departments of [1]Internal Medicine, [2]Gastroenterology and [3]Surgery, UTHealth McGovern Medical School, University of Texas, Houston, Texas, USA

Address for correspondence: Prof. Isis W. Gayed, Department of Diagnostic and Interventional Imaging Nuclear Medicine Section, McGovern Medical School, University of Texas, Houston, Texas, USA.
E-mail: isis.w.gayed@uth.tmc.edu

Submitted: 21-Feb-2020, **Revised:** 06-Apr-2020, **Accepted:** 01-May-2020, **Published:** 22-Aug-2020

Access this article online	
Website: www.annals.in	Quick Response Code
DOI: 10.4103/wjnm.WJNM_21_20	

How to cite this article: Gayed IW, Dawood L, Xu Z, Rizk G, Dupont A, Atta M, *et al.* Improving Hepatobiliary Imaging as a Physiologic Test with Superior Clinical Outcomes. World J Nucl Med 2020;19:353-8.

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.[8]

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.[9-12] 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].

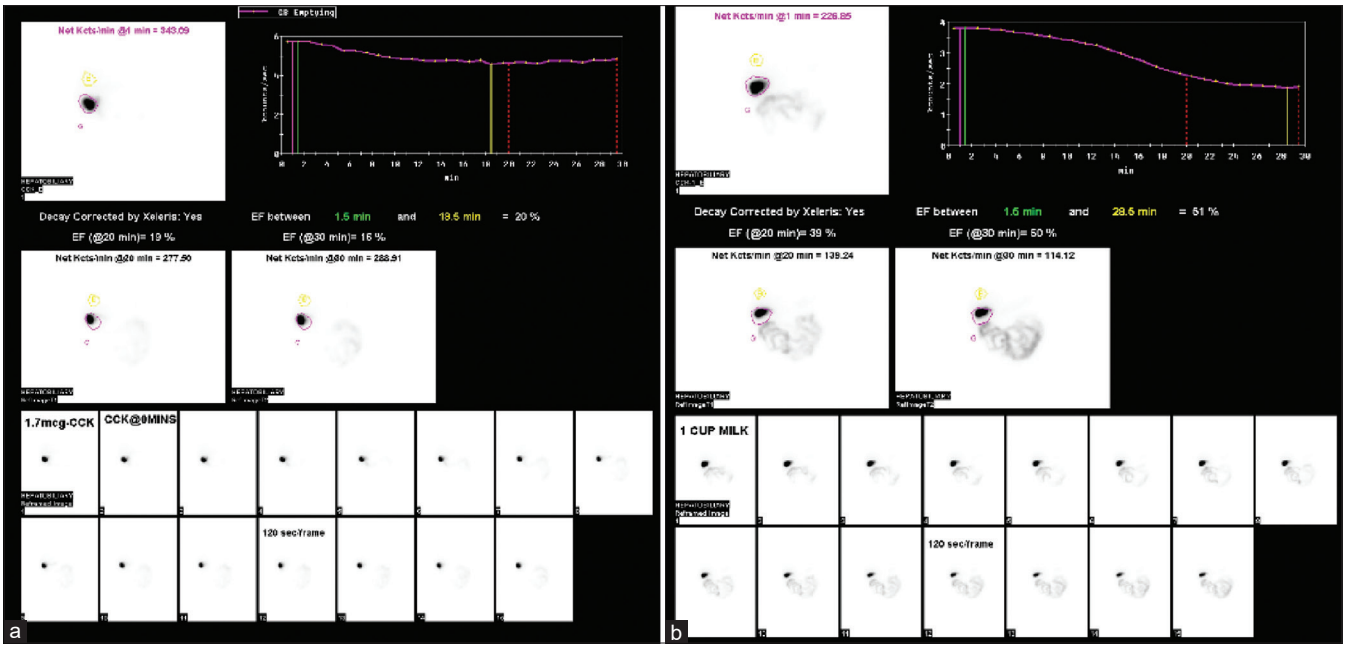

Figure 1: The same patient sequential images and time activity curve of the gallbladder after cholecystokinin administration (a) with a calculated gallbladder ejection fraction 20% and after half and half milk administration (b) with a calculated gallbladder ejection fraction 51%

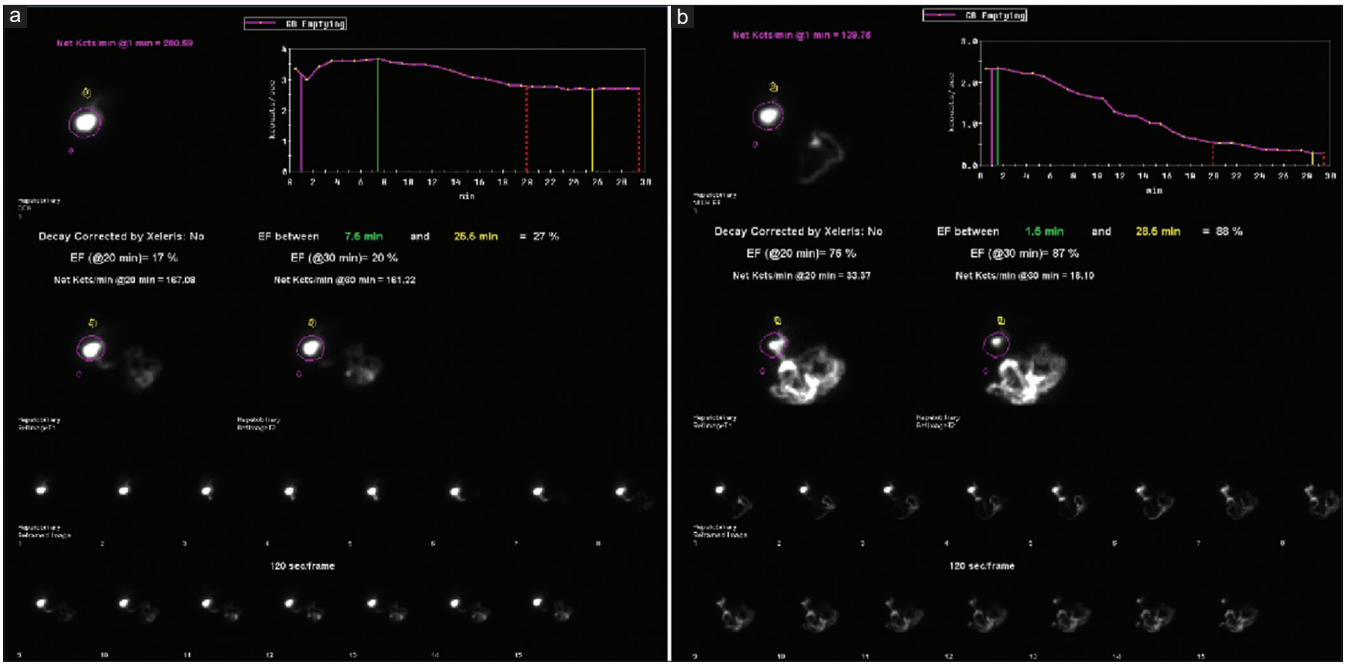

Figure 2: Significant change in gallbladder ejection fraction in the same patient from abnormal 27% after cholecystokinin stimulation (a) to normal 88% after half and half milk stimulation (b)

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

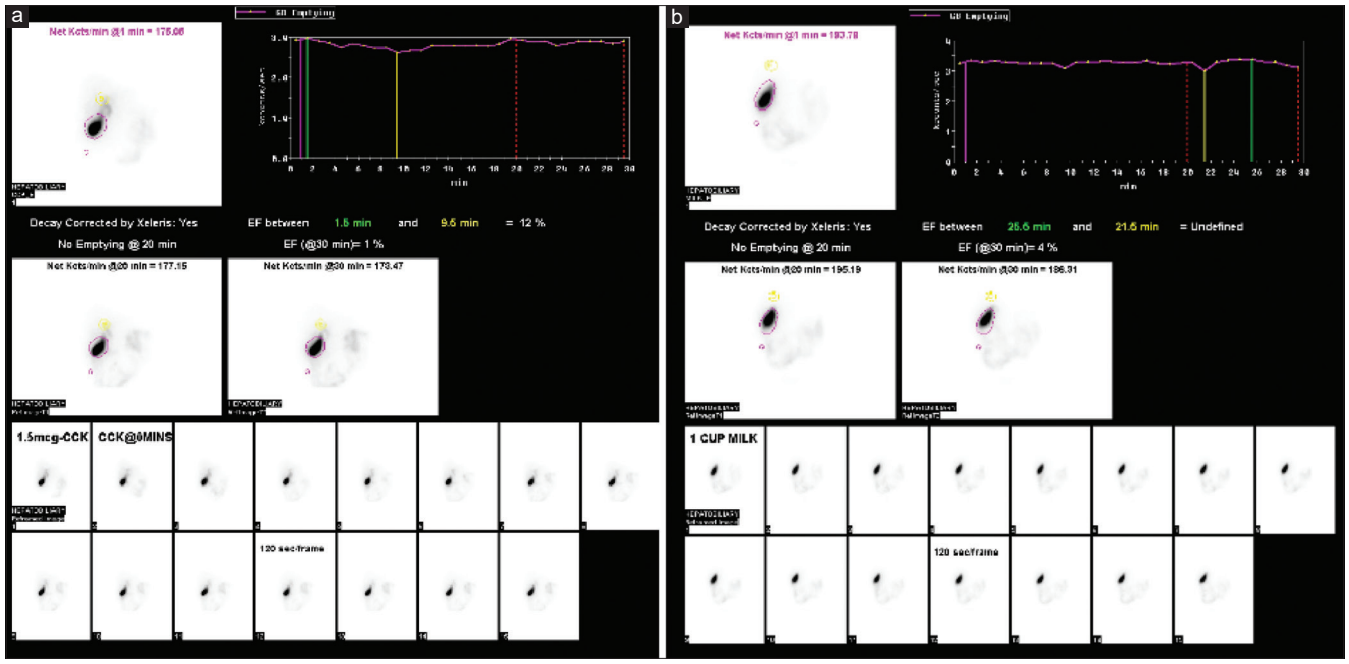

Figure 3: Unchanged abnormal gallbladder ejection fraction in a patient after cholecystokinin stimulation (a) calculated as 12% and after half and half milk stimulation (b) calculated as 4%

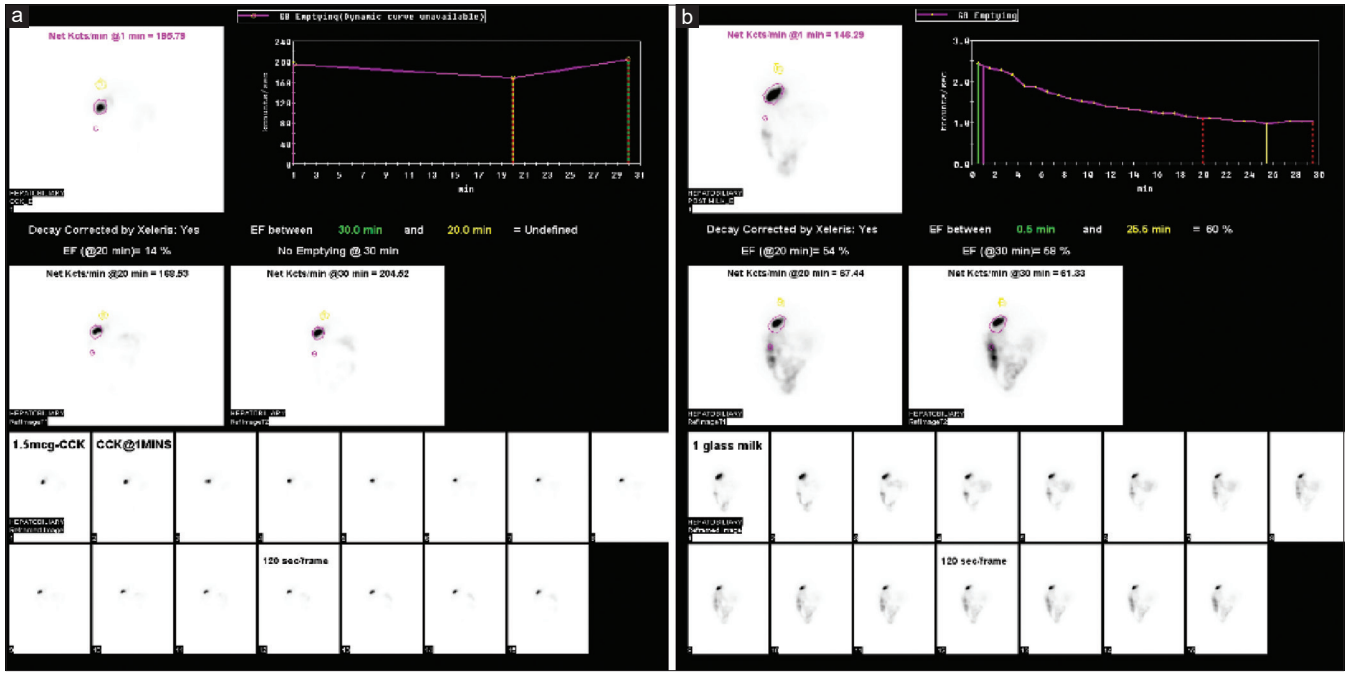

Figure 4: Comparison of the time-activity curve and gallbladder contractility in the same patient after cholecystokinin (a) showing a brief mild contraction followed by relaxation when the cholecystokinin effect fades versus after half-and-half milk (b) showing smooth gradual increasing gallbladder contraction

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

Table 1: The outcome of the patients with abnormal gallbladder ejection fraction both with cholecystokinin and half-and-half milk and those with abnormal gallbladder ejection fraction after cholecystokinin but normal with half and half milk

Clinical outcome	Abnormal GBEF with CCK and HHM (33 patients)[†]		Abnormal GBEF with CCK but normal with HHM (17 patients)[‡]	
	Pain-free or improved pain	Same or worsening pain	Pain-free or improved pain	Same or worsening pain
Cholecystectomy	20	1	2	0
Different diagnosis and/or procedure	4	2	8	5
No intervention	1	3	0	1

[†]2 patients were lost to follow up, [‡]1 patient was lost to follow-up. GBEF: Gallbladder ejection fraction; CCK: Cholecystokinin; HHM: Half and half milk

and/or gallbladder dyskinesia or they were not diagnosed with any definite diagnosis. They remain undetermined if they are false-negative studies with HHM versus not responding to the treatment for these different diagnoses or they are misdiagnosed. Two of these patients had GERD/gastritis; one had elevated liver enzymes; one with chronic pancreatitis; and one with fatty liver.

DISCUSSION

Our study has shown that using HHM results in better gallbladder contractility than using CCK injection over 3 min. Thirty-four percent of the patients demonstrated an increase in their GBEF from below normal limits after CCK injection to the normal limit after HHM stimulation (≥35%). We have also observed a more gradual and continuous slow contractility of the gallbladder after HHM stimulation with a steady smooth decline of the time-activity curve suggestive of a more physiologic response than with CCK injection [Figure 4].

The diagnosis of chronic acalculous cholecystitis has been previously questioned by Lillemoe[1] 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.[14] 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.[15] 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.[16] 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 strength of our study is the design as a prospective study with consecutive enrollment of patients, and only three patients lost to follow-up at 6 months. Many studies have been published in the literature about CCK stimulated hepatobiliary imaging, but they were mostly retrospective studies.[17-19] Limitation of our study that HHM was administered after CCK administration which may raise the question if we are double stimulating the gallbladder with two stimuli one after the other, CCK followed by HHM. Most likely, the effect of CCK should have weaned off by the time we administered HHM since the interval between CCK administration and milk administration is approximately 45 min while the half-life of CCK in the blood is only 2.5 min.[20] Thus, HHM was administered after almost 18–20 half-life of CCK effect. In addition, it is a well-established routine practice in hepatobiliary imaging to administer CCK 30 min before initiation of the hepatobiliary scan in patients who have been fasting for longer than 24 h to clear

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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Lillemoe KD. Chronic acalculous cholecystitis: Are we diagnosing a disease or a myth? Radiology 1997;204:13-4.
2. Westlake PJ, Hershfield NB, Kelly JK, Kloiber R, Lui R, Sutherland LR, *et al*. Chronic right upper quadrant pain without gallstones: Does HIDA scan predict outcome after cholecystectomy? Am J Gastroenterol 1990;85:986-90.
3. Yap L, Wycherley AG, Morphett AD, Toouli J. Acalculous biliary pain: Cholecystectomy alleviates symptoms in patients with abnormal cholescintigraphy. Gastroenterology 1991;101:786-93.
4. Thiels CA, Cima RR, Habermann EB. In response to: Preston JF, Diggs BS, Dolan JP, Gilbert EW, Schein M, Hunter JG. Biliary dyskinesia: A surgical disease rarely found outside the United States. Am J Surg. 2015;209:799-803, Am J Surg 2015;210:963.
5. Krishnamurthy GT, Bobba VR, Kingston E. Radionuclide ejection fraction: A technique for quantitative analysis of motor function of the human gallbladder. Gastroenterology 1981;80:482-90.
6. Gurusamy KS, Junnarkar S, Farouk M, Davidson BR. Cholecystectomy for suspected gallbladder dyskinesia. Cochrane Database Syst Rev 2009;21:1CD007086.
7. Barr RG, Agnesi JN, Schaub CR. Acalculous gallbladder disease: US evaluation after slow-infusion cholecystokinin stimulation in symptomatic and asymptomatic adults. Radiology 1997;204:105-11.
8. Ziessman HA, Tulchinsky M, Lavely WC, Gaughan JP, Allen TW, Maru A, *et al*. Sincalide-stimulated cholescintigraphy: A multicenter investigation to determine optimal infusion methodology and gallbladder ejection fraction normal values. J Nucl Med 2010;51:277-81.
9. Fink-Bennett D, DeRidder P, Kolozsi WZ, Gordon R, Jaros R. Cholecystokinin cholescintigraphy: Detection of abnormal gallbladder motor function in patients with chronic acalculous gallbladder disease. J Nucl Med 1991;32:1695-9.
10. Fotos JS, Tulchinsky M. Oral Cholecystagogue Cholescintigraphy: A Systematic Review of Fatty Meal Options. Clin Nucl Med 2015;40:796-8.
11. Krishnamurthy GT, Brown PH. Comparison of fatty meal and intravenous cholecystokinin infusion for gallbladder ejection fraction. J Nucl Med 2002;43:1603-10.
12. Ziessman HA, Jones DA, Muenz LR, Agarval AK. Cholecystokinin cholescintigraphy: Methodology and normal values using a lactose-free fatty-meal food supplement. J Nucl Med 2003;44:1263-6.
13. Mackie CR, Baxter JN, Grime JS, Hulks G, Cuschieri A. Gall bladder emptying in normal subjects-a data base for clinical cholescintigraphy. Gut 1987;28:137-41.
14. Eckenrode AH, Ewing JA, Kotrady J, Hale AL, Smith DE. HIDA scan with ejection fraction is over utilized in the management of biliary dyskinesia. Am Surg 2015;81:669-73.
15. Goussous N, Maqsood H, Spiegler E, Kowdley GC, Cunningham SC. HIDA scan for functional gallbladder disorder: Ensure that you know how the scan was done. Hepatobiliary Pancreat Dis Int 2017;16:197-201.
16. Morris-Stiff G, Falk G, Kraynak L, Rosenblatt S. The cholecystokin provocation HIDA test: Recreation of symptoms is superior to ejection fraction in predicting medium-term outcomes. J Gastrointest Surg 2011;15:345-9.
17. Ahn KS, Han HS, Cho JY, Yoon YS, Kim C, Lee WW. Long-term follow-up of non-operated patients with symptomatic gallbladder stones: A retrospective study evaluating the role of Hepatobiliary scanning. BMC Gastroenterol 2015;15:136.
18. Goussous N, Kowdley GC, Sardana N, Spiegler E, Cunning-ham SC. Gallbladder dysfunction: How much longer will it be controvertial? Digestion 2014;90:147-54.
19. Delgado-Aros S, Cremonini F, Bredenoord AJ, Camilleri M. Systematic review and meta-analysis: Does gall-bladder ejection fraction on cholecystokinin cholescintigraphy predict outcome after cholecystectomy in suspected functional biliary pain? Aliment Pharmacol Ther 2003;18:167-74.
20. Krishnamurthy S, Cerulli-Switzer J, Chapman N, Gerbail T. Krishnamurthy, comparison of gallbladder function obtained with regular CCK-8 and pharmacy-compounded CCK-8. J Nucl Med 2003;44:499-504.