

Litholytic agents as an alternative treatment modality in patients with biliary dyspepsia

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Abstract

Biliary dyspepsia presents as biliary colic in the absence of explanatory structural abnormalities. Causes include gallbladder dyskinesia, sphincter of Oddi dysfunction, biliary tract sensitivity, microscopic sludges, and duodenal hypersensitivity. However, no consensus treatment guideline exists for biliary dyspepsia. We investigated the effects of medical treatments on biliary dyspepsia.

We retrospectively reviewed the electronic medical records of 414 patients who had biliary pain and underwent cholescintigraphy from 2008 to 2018. We enrolled patients who received litholytic agents and underwent follow-up scans after medical treatment. We divided the patients into the GD group (biliary dyspepsia with reduced gallbladder ejection fraction [GBEF]) and the NGD group (biliary dyspepsia with normal GBEF). We compared pre- and post-treatment GBEF and symptoms.

Among 57 patients enrolled, 40 (70.2%) patients had significant GBEF improvement post-treatment, ranging from $34.4 \pm 22.6\%$ to $53.8 \pm 26.8\%$ ($P < .001$). In GD group ($n=35$), 28 patients had GBEF improvement after medical treatment, and value of GBEF significantly improved from 19.5 ± 11.0 to $47.9 \pm 27.3\%$ ($P < .001$). In NGD group ($n=22$), 12 patients had GBEF improvement after medical treatment, but value of GBEF did not have significant change. Most patients (97.1% in GD group and 81.8% in NGD group) had improved symptoms after medical treatment. No severe complication was reported during treatment period.

Litholytic agents improved biliary colic in patients with biliary dyspepsia. Therefore, these agents present an alternative treatment modality for biliary dyspepsia with or without gallbladder dyskinesia. Notably, biliary colic in patients with gallbladder dyskinesia resolved after normalization of the GBEF. Further prospective and large-scale mechanistic studies are warranted.

Abbreviations: CNU = combination of chenodeoxycholic acid and ursodeoxycholic acid, DISIDA = technetium-99m diisopropyl iminodiacetic acid cholescintigraphy, GB = gallbladder, GBEF = gallbladder ejection fraction, GD = gallbladder dyskinesia, NGD = non-gallbladder dyskinesia, UDCA = ursodeoxycholic acid.

Keywords: biliary dyspepsia, gallbladder dyskinesia, litholytic agent

1. Introduction

Biliary dyspepsia is defined as the presence of biliary pain with no organic, systemic, or metabolic cause.^[1] The causes of biliary dyspepsia include gallbladder dyskinesia (GD), sphincter of Oddi dysfunction, biliary tract sensitivity, microscopic sludges, duodenal hypersensitivity, and parasitic infestation.^[2] Among these causes, GD, also referred to as functional gallbladder (GB) disorder or GB dysfunction, is a rare functional disorder defined

as biliary pain in the absence of gallstone or other structural pathology. The Rome IV criteria describe in detail the diagnostic criteria for biliary pain in the epigastrium and/or right upper quadrant.^[3] The diagnosis of biliary pain due to GD is supported by a low gallbladder ejection fraction (GBEF) on GB scintigraphy and normal laboratory test results.^[3,4] The prevalence of GD has increased due to the introduction of diagnostic modalities such as GB scintigraphy.^[5] Several studies have examined the prevalence

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of biliary dyspepsia. One group reported on the prevalence of biliary pain without gallstone in Italy; 2.0% of the enrolled patients had biliary dyspepsia,^[6] and the prevalence of GD differed according to sex. Other large-population studies showed that GD was more common in females (20.7%) than in males (7.6%).^[7,8]

Medical and surgical therapies can be used to treat biliary dyspepsia according to its cause, but no consensus treatment guideline has been established. A previous study of the efficacy of cholecystectomy for biliary dyskinesia showed that patients who received cholecystectomy exhibited significant symptom improvement compared with nonsurgical patients.^[9]

However, surgery as the primary treatment method for GD is burdensome for elderly patients and those with comorbidities. In such patients, medical treatment for GD is preferred. However, data on the effect of medical treatment on GD are scarce.

We investigated the effects of medical treatments on biliary dyspepsia, with a focus on 2 litholytic agents. The primary outcomes were increased GBEF and symptom improvement after medical treatment.

2. Materials and methods

2.1. Patients

In this retrospective study, we reviewed the electronic medical records of 414 patients who presented with biliary pain and underwent technetium-99m diisopropyl iminodiacetic acid (DISIDA) cholescintigraphy between July 2008 and August 2018, in 6 tertiary hospitals. All reviewed patients were ≥ 18 years and of Korean. Exclusion criteria were patients with no post-treatment DISIDA scan; an organic lesion causing biliary pain; no medical treatment; abnormal laboratory test results (serum levels of aspartate transaminase/alanine transaminase, bilirubin, gamma-glutamyl transferase, amylase, or lipase); acute or episodic symptoms; and history of incomplete electronic medical records. In addition, patients who had impaired mobility, renal insufficiency, electrolyte imbalance, and history of abdominal surgery were also excluded.

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of Gangnam Severance Hospital (IRB No: 3-2019-0244). Informed consent was not required because this study was a retrospective analysis of existing administrative and clinical data.

2.2. Data collection

Data were retrospectively extracted from the electronic medical records of 6 tertiary hospitals. The data included demographic, clinical, laboratory, and imaging parameters, and the findings of upper gastrointestinal endoscopies performed at the time of treatment initiation.

Demographic data included age, sex, body mass index (BMI), and personal and medical histories. Imaging and GBEF data were collected from initial and follow-up DISIDA scans. Imaging parameters included abdominal ultrasonography, abdominal computed tomography, magnetic resonance imaging, and endoscopic ultrasonography. Regarding litholytic agents, we collected data on the type, duration, and side effects of medication. We analyzed data from patients who received 2 litholytic agents: Ursa (ursodeoxycholic acid [UDCA];

Daewoong Pharm. Co. Ltd., Seoul, South Korea) and CNU (magnesium trihydrate salt of chenodeoxycholic acid and ursodeoxycholic acid [CNU]; Myungmoon Pharm. Co., Seoul, South Korea).

2.3. DISIDA scanning

All enrolled patients underwent pre- and post-treatment DISIDA scans, during which GBEF values were measured and recorded. The method used for DISIDA scanning is described in detail below.^[10]

The DISIDA scan was performed after the patient had fasted overnight. Each subject was given 8 mCi DISIDA intravenously under a large-field-of-view gamma camera. Serial hepatobiliary analogue images were obtained at 5, 10, 20, 30, 45, and 60 minutes after the injection or until the GB was adequately filled. Immediately after completion of the filling phase, the patients drank 200 mL milk containing about 13 g fat (130 kcal). Analogue images were recorded 30 minutes after ingestion of the milk. The GBEF was derived by calculating the counts in the GB before and 30 minutes after ingestion of the milk. Background regions over the liver were also generated and subtracted from the GB counts to derive the net GB count.

2.4. Definitions

Biliary dyspepsia defined as biliary colic without any organic, systemic, or metabolic origin. Biliary colic was steady pain in the right upper quadrant and/or epigastric area, lasting for at least 30 minutes according to Rome IV criteria.^[4] To exclude patients, who have organic, systemic, and metabolic origin, we reviewed the result of laboratory and imaging parameters, and the findings of upper gastrointestinal endoscopies. These enrolled patients, who had biliary dyspepsia, were divided into 2 groups according to the results of the initial DISIDA scans. Patients who had reduced initial GBEFs ($< 38\%$) were allocated to the GD group. Patients who had normal initial GBEFs ($\geq 38\%$) were allocated to the non-gallbladder dyskinesia (NGD) group.

After medical treatment, we evaluated the GBEFs and symptoms of the patients. The GBEF was evaluated by follow-up DISIDA scan and classified as showing improvement, no change, or deterioration. The improvement of symptoms after treatment was also evaluated.

2.5. Statistical analysis

Continuous variables are reported as means \pm standard deviations. We used Student *t* test or the Wilcoxon rank-sum test to compare continuous variables between the groups. Categorical variables are reported as numbers and percentages and were compared by Chi-squared test or Fisher exact test. Statistical analysis was performed using the SPSS version 23.0 (IBM Corp., Armonk, NY). Two-tailed *P* values $< .05$ were considered to indicate statistical significance.

3. Results

3.1. Patients

In total, 414 patients underwent DISIDA scans for biliary pain between July 2008, and August 2018. Among these patients, 6 were excluded because their biliary pain was determined to be of

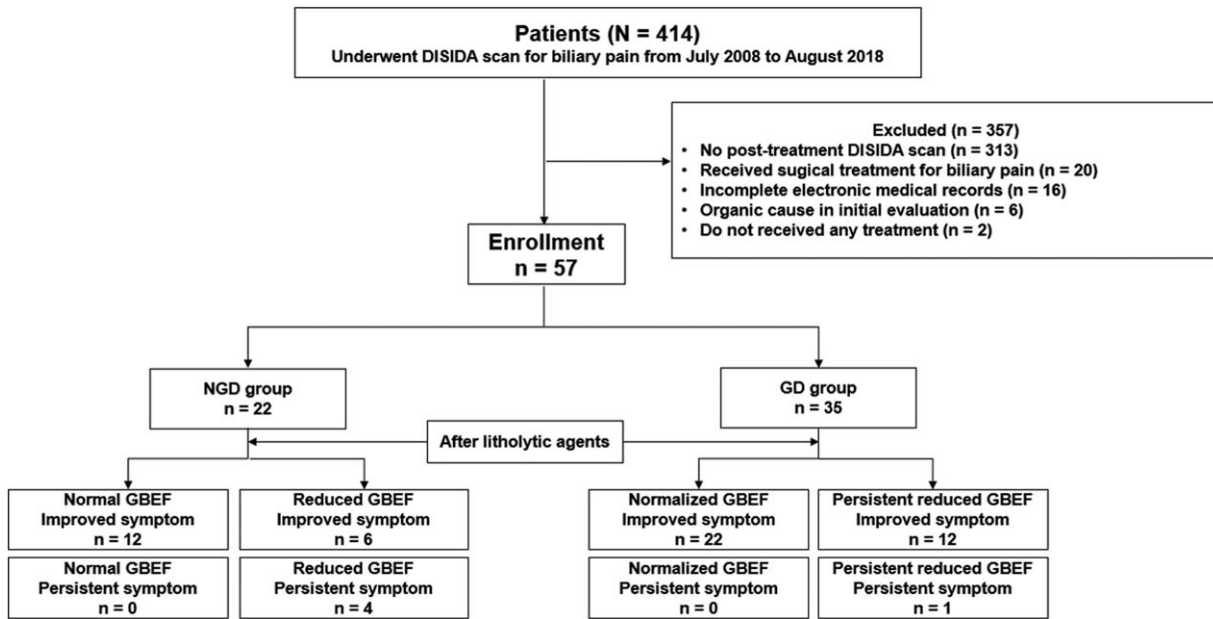


Figure 1. Study flow chart. We enrolled in this retrospective study 57 patients with biliary pain who underwent cholescintigraphy. DISIDA, technetium-99m diisopropyl iminodiacetic acid cholescintigraphy; GB, gallbladder; GBEF, gallbladder ejection fraction; NGD, biliary pain with normal gallbladder ejection fraction; GD, biliary pain with reduced gallbladder ejection fraction.

organic cause. The remaining 408 patients were diagnosed with biliary dyspepsia. Among them, we excluded those with the following characteristics:

- (1) lack of post-treatment DISIDA scan ($n=313$)
- (2) receipt of surgical treatment for biliary pain ($n=20$)
- (3) incompleteness of electronic medical records ($n=16$)
- (4) receipt of no treatment ($n=2$). As a result, 57 patients were enrolled in this study (Fig. 1)

3.2. Baseline characteristics

The mean age of the participants was 46.4 ± 15.9 years, and females were predominant (71.9%). The average BMI was 23.3 ± 5.0 kg/m², and 10 (17.5%) patients were obese according to the Asia-Pacific criteria. Three patients were current smokers, and 9 patients had histories of alcohol consumption. Two and 8 patients had diabetes mellitus and hypertension, respectively (Table 1).

| Variables | All patients (N=57) |
|--|---------------------|
| Age (yr, mean \pm SD) | 46.4 \pm 15.9 |
| Male (n, %) | 16 (28.1) |
| BMI (kg/m ² , mean \pm SD) | 23.3 \pm 5.0 |
| Current smoker (n, %) | 3 (5.3) |
| Alcohol history (n, %) | 9 (15.8) |
| DM (n, %) | 2 (3.5) |
| Hypertension (n, %) | 8 (14.0) |
| Initial DISIDA scan | |
| Pretreatment GBEF (% , mean \pm SD) | 34.4 \pm 22.6 |
| GD diagnoses based on pretreatment GBEF (n, %) | 35 (61.4) |

BMI = body mass index, DISIDA = technetium-99m diisopropyl iminodiacetic acid cholescintigraphy, DM = diabetes mellitus, GB = gallbladder, GBEF = gallbladder ejection fraction, GD = gallbladder dyskinesia.

Table 2 shows the litholytic agents prescribed for biliary dyspepsia. Among the patients, 19 (33.3%) received CNU and 38 (66.7%) received UDCA. The mean treatment duration was 15.6 ± 20.1 months.

3.3. Result of DISIDA scan

On initial DISIDA scans, the mean pre-treatment GBEF was $34.4 \pm 22.6\%$, and 35 (61.4%) patients had GBEFs < 38% (Table 1). Therefore, 35 patients were diagnosed with GD, and the remaining 22 patients were allocated to the NGD group. Mean time interval between initial and follow-up DISIDA scan was 8.6 ± 6.8 months.

The quantitative changes in the GBEF are shown in Table 3. For all patients, the initial mean GBEF ($34.4 \pm 22.6\%$) was significantly lower than that after medical treatment ($53.8 \pm 26.8\%$; $P < .001$). In addition, UDCA significantly increased the GBEF from $29.4 \pm 18.8\%$ to $51.2 \pm 26.4\%$ ($P < .001$) for all

| Variables | All patients (N=57) |
|--|---------------------|
| Litholytic agents (n, %) | |
| CNU | 19 (33.3) |
| UDCA | 38 (66.7) |
| Duration of medication (months, mean \pm SD) | 15.6 \pm 20.1 |
| Improved biliary pain (n, %) | 52 (91.2) |
| GD group | 34/35 (97.1) |
| NGD group | 18/22 (81.8) |
| Complications | |
| Diarrhea | 1 (1.8) |
| Constipation | 1 (1.8) |

CNU = combination of chenodeoxycholic acid and ursodeoxycholic acid, GD = gallbladder dyskinesia, NGD = non-gallbladder dyskinesia, UDCA = ursodeoxycholic acid.

| | Pretreatment | Post-treatment | P-value |
|---------------------|--------------|----------------|---------|
| All patients (n=57) | 34.4 ± 22.6 | 53.8 ± 26.8 | <.001 |
| CNU (n=19) | 44.5 ± 26.4 | 58.9 ± 27.5 | .107 |
| UDCA (n=38) | 29.4 ± 18.8 | 51.2 ± 26.4 | <.001 |
| GD group (n=35) | 19.5 ± 11.0 | 47.9 ± 27.3 | <.001 |
| CNU (n=9) | 21.4 ± 11.8 | 46.4 ± 30.5 | .035 |
| UDCA (n=26) | 18.9 ± 10.8 | 48.4 ± 26.8 | <.001 |
| NGD group (n=22) | 58.1 ± 14.4 | 63.1 ± 23.6 | .401 |
| CNU (n=10) | 65.3 ± 15.9 | 70.2 ± 19.7 | .548 |
| UDCA (n=12) | 52.1 ± 10.2 | 57.2 ± 25.7 | .533 |

CNU=combination of chenodeoxycholic acid and ursodeoxycholic acid, GB=gallbladder, GBEF=gallbladder ejection fraction, GD=gallbladder dyskinesia, NGD=non-gallbladder dyskinesia, UDCA=ursodeoxycholic acid.

patients. Patients receiving CNU treatment also showed a significant difference in the GBEF ($P=.107$). Figure 2 (A) and (B) are pre- and post-treatment GBEF dot plots for all patients.

In the GD group, the mean pre-treatment GBEF ($19.5\% \pm 11.0\%$) was significantly lower than that after medical treatment ($47.9 \pm 27.3\%$, $P < .001$; Table 3). In patients with GD, CNU and UDCA significantly increased the GBEF (Fig. 2D). CNU treatment increased the GBEF from $21.4 \pm 11.8\%$ to $46.4 \pm 30.5\%$ ($P=.035$; Fig. 2E), and UDCA treatment increased the GBEF from $18.9 \pm 10.8\%$ to $48.4 \pm 26.8\%$ ($P < .001$; Fig. 2F). The GBEF did not change significantly in the NGD group ($P=.401$; Table 3, Fig. 2C).

Figure 3 shows representative DISIDA scans of a treatment-responsive patient with GD (A) before and (B) after CNU treatment. This patient's GBEF was 20.1% before treatment and 85.0% after treatment.

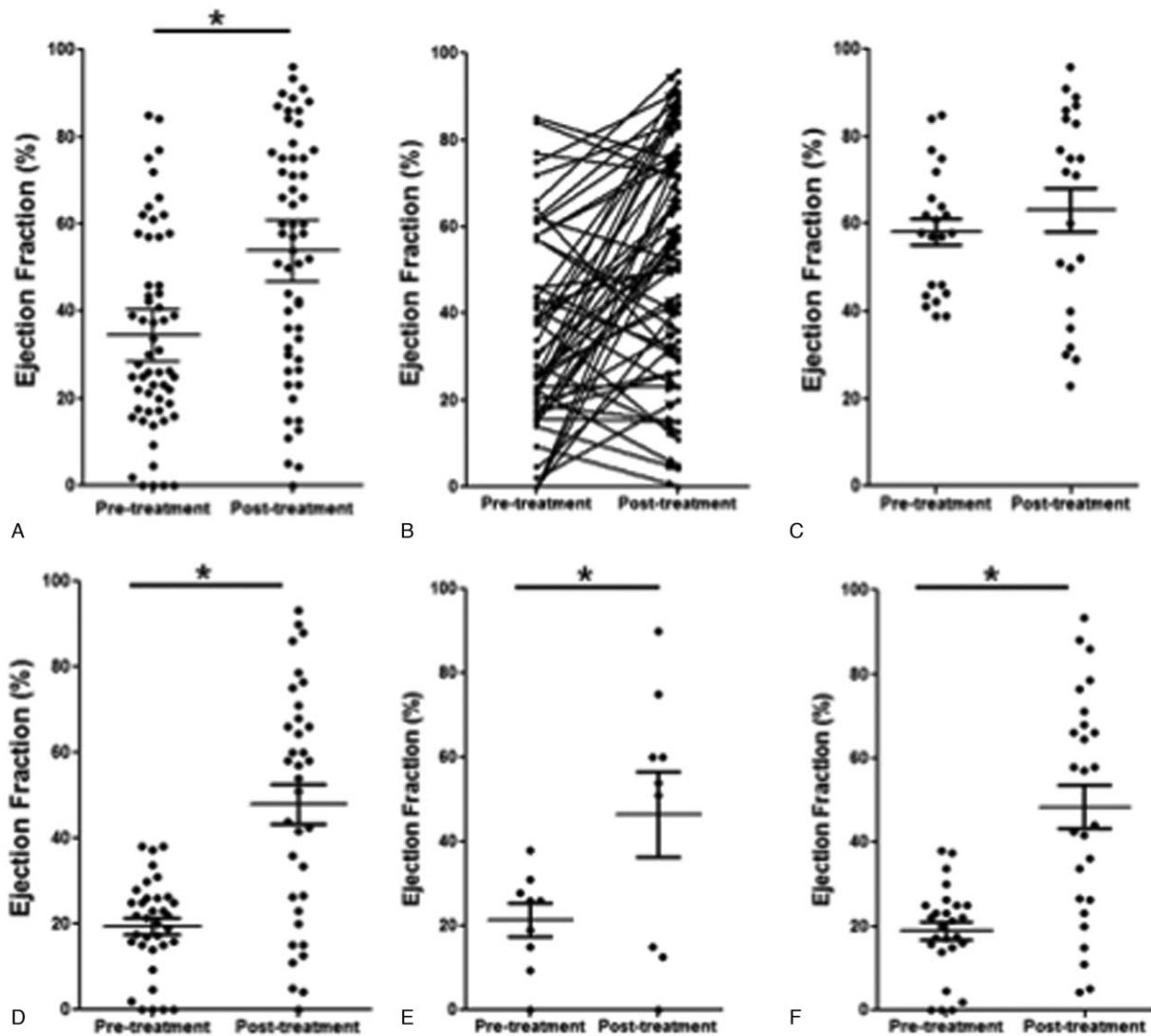


Figure 2. Pre- and post-treatment gallbladder ejection fractions. (A) Dot plot and (B) paired dot plot for all patients. Dot plots for the NGD group (C) and GD group (D). Dot plots for the patients in the GD group who received CNU (E) and UDCA (F). * $P < .05$. GBEF, gallbladder ejection fraction; NGD, biliary pain with normal gallbladder ejection fraction; GD, biliary pain with reduced gallbladder ejection fraction.

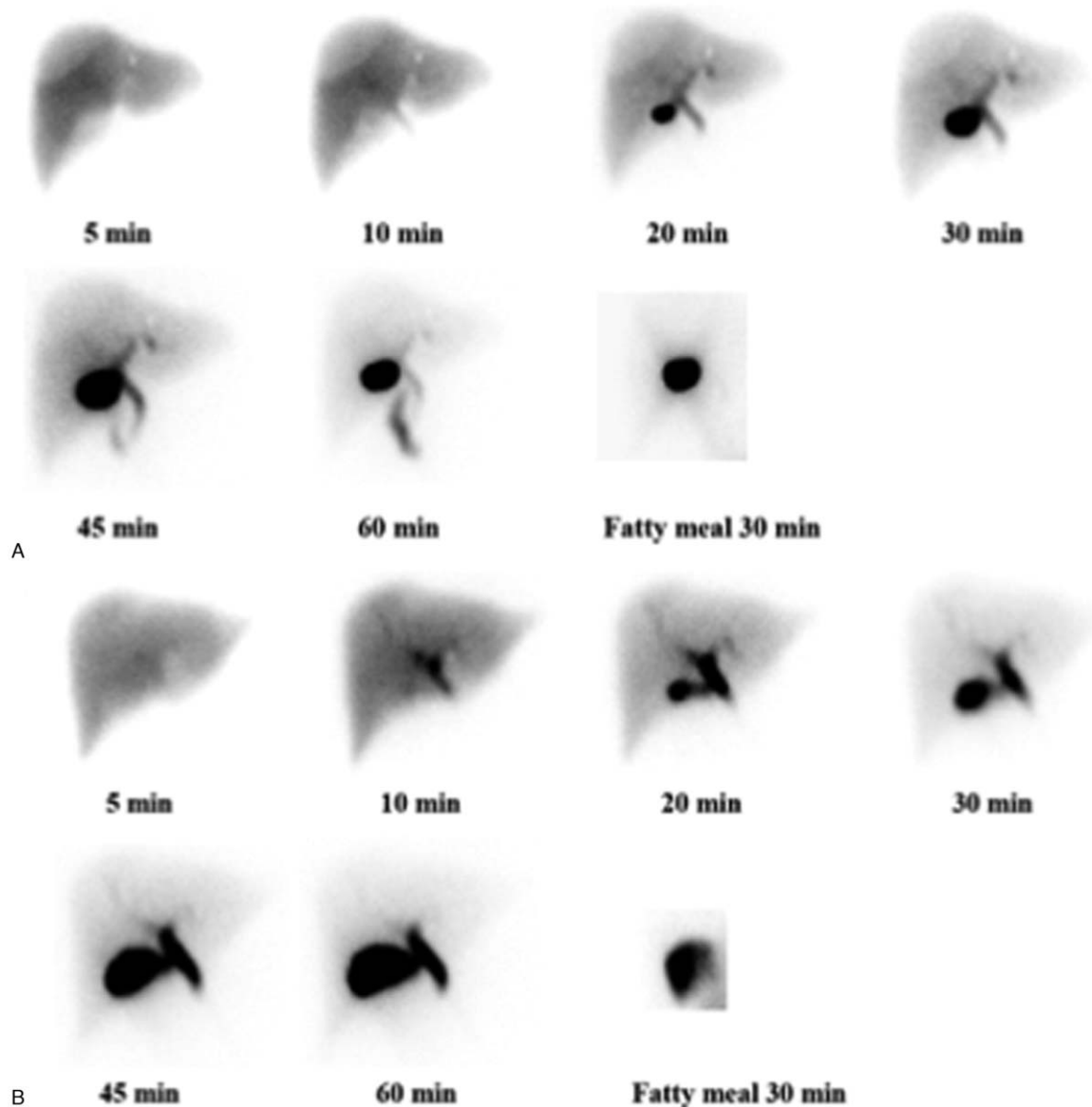


Figure 3. Representative DISIDA scans of a patient with GD with improved GBEF. DISIDA scans (A) before medical treatment (GBEF = 20.1%) and (B) after medical treatment (GBEF = 85.0%). DISIDA, technetium-99m diisopropyl iminodiacetic acid cholescintigraphy; GB, gallbladder; GD, gallbladder dyskinesia; GBEF, gallbladder ejection fraction.

3.4. Symptom improvement after medical treatment

Biliary pain symptoms improved in 52 (91.2%) patients (97.1% in the GD group, 81.8% in the NGD group). The rate of symptom improvement was significantly greater in the GD group than in the NGD group ($P < .001$).

Among the 35 patients with GD, all 22 patients with normalized GBEFs after medical treatment experienced improvement of their biliary pain. Of the 13 patients who had persistent GD (as indicated by their GBEFs) despite medical treatment, 12 patients had improved symptoms and 1 patient had persistent symptoms (Fig. 1).

Two patients had side effects while using UDCA (diarrhea and constipation, respectively). However, these side effects were not serious enough to warrant discontinuation of the treatment.

4. Discussion

We determined that litholytic agents improved symptoms of biliary dyspepsia. In addition, patients with GD experienced significant improvement in symptoms and the GBEF after medical treatment. Although the mechanism of GD is unclear, researchers have made plausible suggestions. First, a narrowed cystic duct can induce incomplete GB emptying, eventually causing chronic cholecystitis and biliary pain.^[11] Another group reported an association between the cystic duct, rather than the common bile duct or sphincter of Oddi, and GB dysfunction.^[12] Second, microlithiasis is associated with GD. One previous study compared GB emptying among 3 groups (healthy controls, patients with gallstones, and patients with microlithiasis).^[13] The GBEF was significantly lower in patients with microlithiasis than

in control patients. Beyond these potential mechanisms, several factors, such as prostaglandin E₂, are also associated with the pathogenesis of GD.^[4,14,15]

Among these factors, we hypothesized that UDCA might have an effect on dissolution of microlithiasis, thereby, improved GD. However, further analysis of bile from these patients is warranted to evaluate the effect of medical treatment with UDCA on microlithiasis, and UDCA was shown to correct this bile abnormality.

We used a GBEF cutoff value for GD of 38%. No cut-off value for GD has been established, although values of 35% to 50% have been set in previous studies.^[16,17] Further research to establish uniform cutoff value for GD should be performed. However, our study will be meaningful to compare incidence of GD and result of our study with other studies, which use cutoff value as 38%.

In patients with GD in this study, the proportion of symptom improvement (97.1%) was not consistent with that of GBEF normalization (80.0%). Whether this effect was due to medical treatment is not certain, because no GBEF cut-off value has been evaluated formally or established.^[4] Patients with GD may respond to medical treatments, such as UDCA, but the sample for this study was too small for such an evaluation. Patients who had biliary pain and normal GBEFs experienced significant improvement in pain symptoms. Interestingly, the GBEF was not significantly changed after treatment. The mechanism of symptom improvement was not clear because of the heterogeneity of the NGD group. The causes of biliary dyspepsia in the NGD group could include sphincter of Oddi dysfunction, biliary tract sensitivity, and microscopic gallstones or sludges.^[18,19]

Our study has several strengths over previous studies. First, biliary pain and GBEF values were required to diagnose GD. Most previous studies that aimed to evaluate treatment effects focused solely on symptom improvement. Symptoms can be subjective, even when evaluated using a pain scale. We evaluated the effects of medication on not only symptoms but also the GBEF, a more objective and reliable measure. Second, our study enrolled patients with GD and NGD. Many patients visit outpatient clinics because of biliary pain located in the epigastrium and/or right upper quadrant. Physicians perform various tests, including laboratory and imaging tests, as part of their initial evaluation. When the results of these tests are normal, many clinicians suspect functional gastrointestinal disorder or irritable bowel syndrome. A previous study showed that the evaluation of GB function is necessary to exclude GD in patients who present with biliary pain.^[20] Our study confirms this finding in a larger number of patients.

This study has several limitations. First, this study was retrospective and sample size was too small. When patients have biliary colic, DISIDA scan is not a routine test in our clinic. Moreover, patients tend to not be performed follow-up DISIDA scan when they recover from symptoms. Because of this small sample size, it is hard to analyze control group. Only 2 patients did not receive any treatment. Prospective and large-scale study is warranted. Second, we evaluated symptoms by retrospectively reviewing patients' electronic medical records. Further investigation of symptoms using a method such as a visual analogue scale is needed because the pain evaluation was subjective. Third, we evaluated the effects of litholytic agents, but did not determine whether medical treatment is superior to surgical treatment. Further study of medical and surgical treatments is thus warranted. Fourth, according to the Rome IV criteria, GD is not the only condition that induces biliary pain; other conditions

(e.g., sphincter of Oddi dysfunction and duodenal hypersensitivity) can also induce biliary pain.^[21] Because we reviewed medical records that included DISIDA scans, we were unable to diagnose these other conditions. For example, manometry for the diagnosis of sphincter of Oddi dysfunction is not a routine test. Therefore, the NGD group was heterogeneous in terms of the causes of biliary dyspepsia.

In conclusion, the litholytic agents UDCA and CNU modulated the GBEF and induced symptom improvement in patients with biliary dyspepsia. In addition, the complication rate of medical treatment was low. Therefore, treatment with litholytic agents may be an alternative to surgical treatment for biliary dyspepsia, especially in patients for whom surgery is contraindicated. Notably, biliary pain resolved after normalization of the GBEF in patients with GD.

Author contributions

Critical revision of the manuscript: S.I.J., D.H.K., S.J., D.K.L.
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Study supervision: S.I.J., D.H.K., D.K.L.
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