Optimal timing for performing percutaneous transhepatic gallbladder drainage and subsequent cholecystectomy for better management of acute cholecystitis

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Abstract

Background: We aimed to clarify the appropriate timing for performing percutaneous transhepatic gallbladder drainage (PTGBD) and cholecystectomy, and the effect of PTGBD on surgical difficulty in acute cholecystitis patients.

Methods: We retrospectively examined 46 patients who underwent laparoscopic cholecystectomy (LC) after PTGBD for acute cholecystitis. We evaluated the duration from acute cholecystitis onset to PTGBD and the appropriate interval from PTGBD to elective LC. Intraoperative blood loss, operating time, rate of conversion to open surgery, and rate of severe adhesion were the objective and subjective measures.

Results: Based on the cut-off value calculated using the Youden index, the group with a duration from acute cholecystitis onset to PTGBD of ≤73.5 hours had a significantly shorter operating time (127.5 min vs. 180.0 min, p=0.007), lower rate of severe adhesion (3/20 vs. 14/26, p=0.007), and lower rate of conversion to open surgery (2/20 vs. 13/26, p=0.004); moreover, the interval from PTGBD to elective LC did not significantly differ between these groups.

Conclusion: The most important predictor of successful LC following PTGBD for acute cholecystitis was a duration from acute cholecystitis onset to PTGBD of ≤73.5 hours. Hence, PTGBD should be performed immediately in cases where early cholecystectomy is not indicated.

INTRODUCTION

Laparoscopic cholecystectomy (LC) was previously not considered to be suitable for the treatment of acute cholecystitis. However, given the advancements in the techniques and

instruments, and after the establishment of a critical view of safety for the dissection of Calot's triangle (introduced by Strasberg et al.) [1], LC is now accepted as a safe surgical technique for acute cholecystitis when performed by an experienced surgeon [2].

The Tokyo Guidelines 2013 (TG13) presented a management strategy for acute cholecystitis based on an assessment of the severity, which includes infusion therapy, antibiotic treatment, surgery, and gallbladder drainage [3]. Early LC, within 72 hours of onset, is considered the first-line treatment in patients with grade I (mild) acute cholecystitis. Moreover, early cholecystectomy, within 72 hours of onset, is required in patients with grade II (moderate) acute cholecystitis; however, in some grade II patients, it is difficult to remove the gallbladder surgically due to the presence of severe inflammation. Such severe local inflammation of the gallbladder can be identified by factors such as duration of symptoms for >72 hours, white blood cell count >18,000/μL, and a palpable tender mass in the upper right abdominal quadrant. Continued medical treatment, including drainage of the contents of the swollen gallbladder by percutaneous transhepatic gallbladder drainage (PTGBD) or surgical cholecystostomy, is preferable, followed by delayed cholecystectomy after the improvement of inflammation. Grade III (severe) acute cholecystitis is accompanied by organ dysfunction, and requires immediate gallbladder drainage [2, 3]. TG13 recommends PTGBD as the standard drainage method [4, 5].

PTGBD quickly improves the symptoms of acute cholecystitis, and is known to be an effective option in critically ill patients [2]. However, the optimal timing for performing cholecystectomy after PTGBD is controversial due to a lack of any strong evidence [2]. Some hospitals perform cholecystectomy after PTGBD, following an interval of several days [6, 7], whereas others ensure an interval of 2 weeks [8]. Furthermore, the optimal timing for performing PTGBD after the onset of acute cholecystitis and the effect of PTGBD on surgical difficulty remain unknown. Therefore, in the present study, we aimed to clarify the optimal timing for

performing PTGBD and cholecystectomy, and the effect of PTGBD on surgical difficulty in patients with acute cholecystitis.

METHODS

Patients

This study was a retrospective analysis of patients who underwent LC after PTGBD for acute cholecystitis at our hospital from April 1993 to August 2014. Using the TG13 diagnostic criteria, acute cholecystitis was diagnosed based on clinical symptoms, blood test results, and findings on ultrasonography and computed tomography. Patients who had a history of upper abdominal surgery, history of recurrent cholecystitis, serious comorbidity, or internal use of anticoagulants were excluded from the study. Informed consent was waived due to the retrospective nature of this study.

Method

At our hospital, LC is routinely performed by surgeons certified by the Japan Surgical Society; decisions to convert from LC to open surgery were made by these surgeons in all cases. Currently, at our hospital, surgeons certified by the Japanese Society of Hepato-Biliary-Pancreatic Surgery are always on call [9]. Objective and subjective measures were used to assess the difficulty of performing LC. Intraoperative blood loss, operating time, and rate of conversion to open surgery were selected as objective measures, whereas the rate of severe adhesion was used as a subjective measure.

Because there are no quantitative evaluation methods for adhesion, patients were classified as having severe adhesion if the surgeon reported (1) difficulty in establishing the critical view of safety or (2) difficulty in removing the entire gallbladder from the liver bed. All the other patients were defined as having mild adhesion. The criteria for conversion

to open surgery were the presence of the above 2 items, and an operating time of >3 hours until the confirmation of the anatomy of the cystic artery and duct.

Relationship between the duration from onset of acute cholecystitis to PTGBD and conversion to open surgery

The duration from onset of acute cholecystitis to PTGBD was compared in patients who underwent successful laparoscopic surgery (laparoscopic group) and in those who underwent conversion to open surgery (conversion group). Thereafter, receiver operating characteristic (ROC) analysis was performed. The area under the curve (AUC) was evaluated to determine the accuracy of the relationship between the duration from onset of acute cholecystitis to PTGBD and surgical procedure (low accuracy: [AUC, 0.5-0.7]; moderate accuracy: [AUC, 0.7-0.9], and high accuracy [AUC, 0.9-1]) [10, 11]. To examine whether the timing of PTGBD had an influence on the results of elective surgery, patients were divided into 2 groups: early PTGBD (duration from onset of acute cholecystitis to PTGBD ≤73.5 hours) and late PTGBD (duration from onset of acute cholecystitis to PTGBD >73.5 hours). The cut-off value was calculated by using the Youden Index [12].

Appropriate interval from PTGBD to elective LC

The interval from PTGBD to elective LC was determined in all patients. Because several papers have reported the cut-off value for the interval from PTGBD to elective LC as 14 days [6-8], the patients in the present study were assigned to groups based on an interval of <14 days and ≥14 days. Thereafter, the relationship between the interval from PTGBD to elective LC and difficulty of LC was examined.

Pathologic findings

Pathologic findings of each resected gallbladder that underwent PTGBD were evaluated. Pathologic findings were classified according to the TG13 criteria [13]: stage I (edematous cholecystitis, 2-4 days), stage II (necrotizing cholecystitis, 3-5 days), stage III (suppurative cholecystitis, 7-10 days), and chronic cholecystitis. The timing of stage I (2-4 days) is in agreement with the optimal timing for performing cholecystectomy for acute cholecystitis, as recommended by the TG13 criteria [13]. Therefore, the patients were assigned to 2 groups based on the pathologic findings: stage I and other. Thereafter, the 2 groups were compared with regard to the presence of a duration from onset of acute cholecystitis to PTGBD of ≤73.5 hours (>73.5 hours is a predictor of conversion to open surgery in this study), rate of the interval from PTGBD to elective LC of <14 days, and inflammatory response (white blood cell count, C-reactive protein level) before PTGBD.

Statistical analysis

Numerical data were expressed as median (range), and evaluated by using the Mann-Whitney *U* test. The rates of conversion to open surgery and of severe adhesion were assessed by using the chi-square test. Analyses were conducted using SPSS version 23 (SPSS, Inc., Chicago, IL, USA). P values of <0.05 were considered statistically significant.

RESULTS

Of the 46 patients included in this study, 33 (71.7%) were male, and the median age was 67.0 years. Severity grades I, II, and III were observed in 14, 26, and 6 patients, respectively. The median duration from onset of acute cholecystitis to PTGBD was 78.0 hours, median interval from PTGBD to elective LC was 15.0 days, and rate of severe adhesion was 37.0% (17/46). Of the 17 cases of severe adhesion, establishing the critical view of safety was difficult in 15 and removing the entire gallbladder from the liver bed was difficult in 2. The rate of

conversion to open surgery was 32.6% (15/46). PTGBD was performed by expert doctors in our department and was technically successful in all patients; PTGBD-related adverse events and perioperative complications did not occur. The characteristics of the study participants are shown in Table 1.

Relationship between the duration from onset of acute cholecystitis to PTGBD and conversion to open surgery

A comparison between the laparoscopic and conversion groups revealed that the conversion group had a significantly longer duration from onset of acute cholecystitis to PTGBD (123 hours [range, 77-168 hours] vs. 65 hours [range, 42-98 hours], p = 0.004) (Fig. 1). The AUC for the relationship between the duration from onset of acute cholecystitis to PTGBD and conversion to open surgery was 0.76 (moderate accuracy), confirming that the duration from onset of acute cholecystitis to PTGBD could be used as a predictor of conversion to open surgery. The cut-off value according to the Youden Index was calculated as 73.5 hours (Figs. 1, 2). A comparison between the groups based on the cut-off value showed that the group with a duration from onset of acute cholecystitis to PTGBD of ≤73.5 hours had less intraoperative blood loss (2.5 g [range, 1.0-87.5 g] vs. 52.5 g [range, 5.0-157.5 g], p = 0.054), significantly shorter operating time (127.5 min [range, 88.8-205.8 min] vs. 180.0 min [range, 141.0-244.0 min], p = 0.007), significantly lower rate of severe adhesion (3/20 [15.0%] vs. 14/26 [53.9%], p = 0.007), and significantly lower rate of conversion to open surgery (2/20 [10.0%] vs. 13/26 [50.0%], p = 0.004) (Table 2).

Appropriate interval from PTGBD to elective LC

A comparison between the groups based on the interval from PTGBD to elective LC of <14 days or ≥14 days revealed a significant difference in the rate of severe adhesion (11/21 [52.4%]

vs. 6/25 [24.0%], p = 0.047). However, there were no significant differences in intraoperative blood loss (50.0 g [range, 2.5-140.0 g] vs. 20.0 g [range, 0.0-102.5 g], p = 0.298), operating time (180.0 min [range, 117.5-240.0 min] vs. 145.0 min [range, 116.5-215.0 min], p = 0.337), or rate of conversion to open surgery (8/21 [38.1%] vs. 7/25 [28.0%], p = 0.467) between the groups (Table 3).

Pathologic findings

A comparison between the groups based on the pathologic findings (stage I or other) revealed that the stage I group (edematous cholecystitis) had a significantly lower rate of severe adhesion (0/23 [0.0%] vs. 17/23 [74.0%], p < 0.001) and a significantly higher rate of a duration from onset of acute cholecystitis to PTGBD of ≤73.5 hours (14/23 [60.9%] vs. 6/23 [26.0%], p < 0.017). However, there were no significant differences in the rate of the interval from PTGBD to elective LC of <14 days (9/23 [39.1%] vs. 12/23 [52.2%], p = 0.375) or inflammatory response (white blood cell count: 12,400/μL [range, 6300-15,100/μL] vs. 14,400/μL [range, 10,500-17,400/μL], p = 0.282; C-reactive protein level: 14.1 mg/dL [range, 4.1-21.5 mg/dL] vs. 16.0 mg/dL [range, 6.5-25.1 mg/dL], p = 0.652) between groups (Table 4).

DISCUSSION

The optimal treatment for acute cholecystitis is early cholecystectomy. However, the development of an established surgical management strategy based on disease severity is required [2]. Early LC for acute cholecystitis has been shown to be preferable based on the rate of conversion to open surgery, rate of complications, and duration of hospitalization [14-16]. Although the TG13 criteria recommend that cholecystectomy should be performed immediately after admission, particularly within 72 hours of the onset of acute cholecystitis [2], the perioperative mortality rates in elderly or critically ill patients have been reported

to be high [16]. Moreover, early LC for acute cholecystitis is performed less frequently than is currently recommended due to the scarcity of surgeons [17-19]. Thus, PTGBD is considered as a safe alternative, especially in surgically high-risk populations [5], and can help manage the scheduling of the elective LC. There have been numerous studies on the timing of cholecystectomy following PTGBD, but none have considered the duration from onset of acute cholecystitis to PTGBD. Thus, the appropriate interval from PTGBD to elective LC and the effect of PTGBD on the difficulty of LC remain controversial.

In the present study, there were no significant differences in intraoperative blood loss, operating time, or conversion to open surgery between groups based on an interval from PTGBD to elective LC of <14 days or ≥14 days. In contrast, the group of patients with a duration from onset of acute cholecystitis to PTGBD of ≤73.5 hours had less intraoperative blood loss, significantly shorter operating time, significantly lower rate of severe adhesion, and significantly lower rate of conversion to open surgery compared with patients with a duration from onset of acute cholecystitis to PTGBD of >73.5 hours. These findings indicate that the most important predictor of successful elective LC in a patient undergoing PTGBD is not the interval from PTGBD to elective LC, but instead a duration from onset of acute cholecystitis to PTGBD of ≤73.5 hours.

Furthermore, it is interesting to note that pathologic findings were affected not by the interval from PTGBD to elective LC, but by the duration from onset of acute cholecystitis to PTGBD. To our knowledge, this seems to be the first report to examine the pathologic findings of acute cholecystitis after PTGBD and demonstrate a causal relationship between duration from onset of acute cholecystitis to PTGBD and difficulty of LC. Because pathologic findings had a strong association with the duration from onset of acute cholecystitis to PTGBD of ≤73.5 hours, we believe that PTGBD may stop the progression of acute cholecystitis and prevent the spread of inflammation to the surrounding tissue. Importantly, we also noted that the effect

of performing PTGBD within 73.5 hours of onset on surgical difficulty was minimal. However, physicians cannot control the time from symptom onset to hospital presentation. Accordingly, physicians should aim to decide the management for acute cholecystitis immediately based on the TG13 Guidelines [20] when patients with acute cholecystitis are admitted to the hospital and are considered to be unable to undergo early LC. The management can reduce surgical difficulty of acute cholecystitis.

The TG13 criteria recommend that patients with grade II acute cholecystitis in whom more than 72 hours have elapsed since symptom onset, should undergo PTGBD. However, our results revealed that PTGBD performed >73.5 hours from onset may not improve the difficulty of LC. Moreover, the TG13 criteria did not clarify the optimal timing for performing elective cholecystectomy after PTGBD. Our results revealed that the interval from PTGBD to elective LC did not influence the difficulty of LC. Moreover, the interval from PTGBD to elective LC did not affect the pathologic findings. Byrne et al. performed a retrospective study of 45 patients who underwent PTGBD because they could not undergo cholecystectomy due to poor general conditions. They reported that 36 patients (78%) improved clinically within 5 days, and that the procedure was an effective alternative to surgery [21]. However, PTGBD can cause procedure-related adverse events, such as increased duration of hospitalization, higher medical costs, pain, lower quality of life, bile leakage, stent migration into the gallbladder or intra-abdominal space, and deviation of the stent from the gallbladder [5]. Therefore, we believe that a long interval from PTGBD to elective LC is not recommended. On the other hand, Han et al reported that a group of patients with an interval from PTGBD to elective LC of <72 hours had a significantly longer operating time and higher rate of perioperative complications compared with a group of patients with an interval from PTGBD to elective LC of >72 hours [22]. It is assumed that early LC after PTGBD may be associated with greater surgical difficulty in cases where the duration from onset of acute cholecystitis to PTGBD is not considered.

We recommend that patients with grade I or II acute cholecystitis who cannot undergo early LC within 72 hours of symptom onset should undergo PTGBD as soon as possible. Although we did not aim to achieve early PTGBD in the present study, cases in which early PTGBD was performed by an expert doctor did not show any PTGBD-related adverse events. Moreover, PTGBD is considered to be a safe alternative to surgery, especially in high-risk populations [5]. Therefore, we believe that early PTGBD performed by an expert doctor is safe. The application of PTGBD in cases of acute cholecystitis wherein more than 73.5 hours have elapsed since symptom onset can still improve the patient's condition through the beneficial effects of PTGBD. Nevertheless, we predict that, in such cases, the effects are limited.

Although PTGBD is recommended as a reliable drainage method, percutaneous transhepatic gallbladder aspiration (PTGBA) may be required in patients who are at risk for self-removal of the PTGBD tube due to decreased comprehension or those who cannot undergo PTGBD for some reason. In patients with a stable condition in whom the LC is delayed due to the scarcity of surgeons, PTGBA can be used to prevent the spread of inflammation to the surrounding tissue.

We conclude that the difficulty of performing LC following PTGBD for acute cholecystitis is dependent on the duration from onset of acute cholecystitis to PTGBD. In addition, the timing of LC after PTGBD should be determined according to the situation of each hospital.

The results obtained in this study suggest that the most important predictor of successful LC following PTGBD for acute cholecystitis is duration from onset of acute cholecystitis to PTGBD of ≤73.5 hours. Therefore, PTGBD should be performed immediately in cases where early cholecystectomy is not indicated, especially in cases with grade II acute cholecystitis; moreover, the indication for cholecystectomy should be determined promptly in such cases. In order to validate these findings, a prospective multicenter study should be performed.

Conflicts of interest

None.

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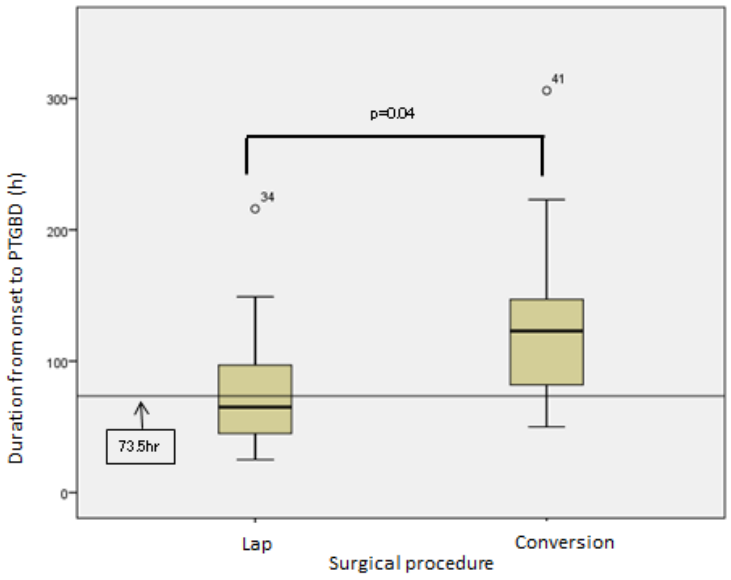

Fig. 1. Box plot of the duration from onset of acute cholecystitis to percutaneous transhepatic gallbladder drainage (PTGBD) and surgery. The horizontal line indicates the cut-off value of the duration from onset of acute cholecystitis to PTGBD, calculated by receiver operating characteristic curve analysis.

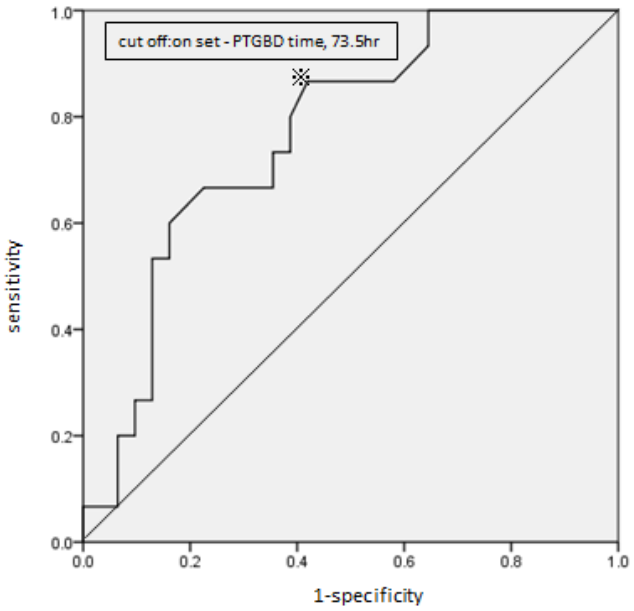

Fig. 2. Receiver operating characteristic curve analysis of the duration from onset of acute cholecystitis to percutaneous transhepatic gallbladder drainage (PTGBD) and conversion to open surgery. The area under the curve is 0.76. The cut-off value was calculated as 73.5 hours according to the Youden index (※).

Table1 Characteristics of participants

	n=46
Age [y]	67.0(62.0-77.3)
Sex (M:W)	33:13
Severity (Ⅰ/Ⅱ/Ⅲ)	14/26/6
Duration from onset to PTGBD [h]	78.0(49.5-123.0)
Interval from PTGBD to elective LC [day]	15.0(8.5-31.25)
Intraoperative blood loss [g]	25.0(1.0-112.5)
Operating time [min]	162.5(118.75-231.0)
Adhesion (Mild:Severe)	29:17
rate of severe adhesion	37.0%
Procedure (Lap:Convert)	31:15
rate of conversion to open surgery	32.6%
WBC [/μL]	13050.0(9125.0-17400.0)
CRP [mg/dl]	14.6(4.1-21.5)

Median (IQR,interquartile range)
Lap: laparoscopic cholecystectomy
Conversion: conversion to open surgery
PTGBD: percutaneous transhepatic gallbladder drainage
Duration from onset to PTGBD:duration from onset of acute cholecystits to PTGBD
WBC: white blood cell count
CRP: c-reactive protein level

Table2 Relationship between the duration from onset to PTGBD and difficulty of LC

	Duration from onset to PTGBD		
	≤73.5 hours (n=20)	>73.5 hours(n=26)	p-Value
Intraoperative blood loss [g]	2.5(1.0-87.5)	52.5(5.0-157.5)	p=0.054
Operating time [min]	127.5(88.8-205.75)	180.0(141.0-244.0)	p=0.007
Adhesion (Mild:Severe) rate of severe adhesion	17:3 15.0%	12:14 53.9%	p=0.007
Surgical procedure (Lap:Conversion) rate of conversion to open surgery	18:2 10.0%	13:13 50.0%	p=0.004

Median(IQR)
Data were calculated using the Mann-Whitney U test or Pearson's chi-square test
PTGBD: percutaneous transhepatic gallbladder drainage
Lap: laparoscopic cholecystectomy
Conversion: conversion to open surgery

Table3 Relationship between interval from PTGBD to elective LC and difficulty of LC

	Interval from PTGBD to elective LC		
	<14 days (n=21)	≥14 days (n=25)	p-Value
Intraoperative blood loss [g]	50.0(2.5-140.0)	20.0(0.0-102.5)	p=0.298
Operating time [min]	180(117.5-240.0)	145.0(116.5-215.0)	p=0.337
Adhesion (Mild:Severe) rate of severe adhesion	10:11 52.4%	19:6 24.0%	p=0.047
Surgical procedure (Lap:Conversion) rate of conversion to open surgery	13:8 38.1%	18:7 28.0%	p=0.467

Median(IQR)
Data were calculated using the Mann-Whitney U test or Pearson's chi-square test
LC: laparoscopic cholecystectomy
PTGBD: percutaneous transhepatic gallbladder drainage
Lap: laparoscopic
Conversion: conversion to open surgery

Table4 Pathologic findings

	Pathologic findings		
	Stage I (n=23)	Other (n=23)	p-Value
Adhesion (Mild : Severe) rate of severe adhesion	23:0 0.0%	6:17 74.0%	p<0.001
Duration from onset to PTGBD(≤73.5 h : >73.5 h) rate of ≤ 73.5 hours	14:9 60.9%	6:17 26.0%	p=0.017
Interval from PTGBD to elective LC (<14 days:≥14 days) rate of <14 days	9:14 39.1%	12:11 52.2%	p=0.375
WBC [/μL]	12400.0(6300.0-15100.0)	14400.0(10500.0-17400.0)	p=0.282
CRP [mg/dl]	14.1(4.1-21.5)	16.0(6.5-25.1)	p=0.652

Median (IQR)
Data were calculated using the Mann-Whitney U test or Pearson's chi-square test
Duration from onset to PTGBD:duration from onset of acute cholecystits to PTGBD
WBC: white blood cell count
CRP: c-reactive protein level