An Investigation of the Optimal Timing of Surgery after Preoperative Gallbladder Drainage for Acute Cholecystitis

Kimihiko Ueno¹, Tetsuo Ajiki², Hiroaki Kominami¹, Kentaro Kawasaki¹, Masahiro Samizo¹,
Hiromi Maeda¹

Corresponding author:

Kimihiko Ueno, MD
Department of Surgery
Kobe Rousai Hospital 4-1-23
Kagoikedori Cyuuou-ku Kobe-city
Hyogo 651-0053 Japan
Tel: 078-382-6302
Fax: 078-382-6307
E-mail: kueno.rhmn@gmail.com

¹Department of Surgery, Kobe Rousai Hospital 4-1-23 Kagoikedori Cyuuou-ku Kobe-city Hyogo, Japan

²Department of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-chou Cyuuou-ku Kobe-city Hyogo, Japan

ABSTRACT

Background: The optimal timing of surgery is still controversial when preoperative gallbladder drainage (PGD) has been performed for AC.

Method: Between 2010 and 2015, 77 AC patients, who consecutively underwent surgery, were divided into two groups. One was the group on which PGD were performed (n=39), and the other was patients that underwent emergency operations (EO) without PGD (n=38). The PGD group was further divided into two groups: one with the period from drainage to surgery of ≤ 14 days (PGD-E: n=17) and in the other the period was >14 days (PGD-D: n=22). The surgical outcomes were compared between these groups.

Results: The blood loss of the PGD group was significantly less (159.7/354.3 ml : $p=0.028$) compared to the EO group. In the PGD-E group the total hospital stay was significantly shorter than that of the PGD-D group (29/40.8 days : $p=0.041$). There were no significant differences between PGD and EO when limited to patients who underwent laparoscopic cholecystectomy (LC).

Conclusion: Surgery within 14 days after PGD might be as safe as surgery over 14 days after PGD. With regard to shortening the total hospital stay, surgery within 14 days after PGD might be recommendable.

Key words: acute cholecystitis, preoperative gallbladder drainage, cholecystectomy

INTRODUCTION

The consensus has generally been that the optimal timing of operations for acute cholecystitis (AC) is within 72hrs from onset, as indicated by Tokyo Guideline 2013 (TG13). (1,2) The usefulness of early operations has been often previously reported, (3-13) and in principle we perform surgery as soon as possible for AC. However, there are some cases in which preoperative gallbladder drainage (PGD) should precede surgery due to the high risk to the patient, severity of AC or difficult situations of emergency operation (EO) within 72hrs from the onset such as the hospital system and a lack of surgeons. (10) Here it becomes a problem in

Received: 08.12.2017

Accepted: 15.12.2017

that the optimal timing of surgery after PGD is not specified in TG13 for AC, resulting in controversy over the optimal timing. With regard to this issue, some reports recommend early surgery, (14) others encourage delayed surgery (15,16) while others found that there were no differences between early and delayed surgery for patients with PGD. (17,18) However in delayed surgery there are some problems for patients such as recurrence of cholecystitis, increased disease duration and total hospital stay extension because of the waiting period until the surgery. Moreover for the patients with retaining percutaneous transhepatic gallbladder drainage (PTGBD), the quality of life is reduced due to the drainage tube. (17,18)

Generally when EO for AC was performed, a tendency of increased blood loss was observed. (7, 8) However, since connective tissue around the gallbladder is mainly edematous in the acute phase, the structure of the layers of tissue is relatively easy to recognize. On the other hand, although the amount of bleeding during the delayed surgery is relatively small, the structure of the layers is often difficult to recognize. Thus there are advantages and disadvantages in early and delayed surgery.

Another problem of surgery for AC is that the number of patients taking anticoagulant drugs because of various heart diseases has recently increased. (19) In surgery on patients taking anticoagulant drugs for AC, an increase in blood loss is a concern. In such cases a hypothesis has been raised that the washout period of anticoagulant drugs may be obtained by PGD, and as a result there is a possibility that blood loss during the operation might be decreased.

Therefore in this study, we evaluated the optimal timing of surgery after PGD for AC to compare the surgical results between early surgery (≤ 14 days from PGD to surgery) and delayed surgery (> 14 days) for patients who underwent PGD. Moreover in AC patients taking anticoagulant drugs we estimated the efficacy and the usefulness of PGD for surgical outcomes between PGD and EO.

METHODS

Patients

A retrospective analysis was carried out on patients on whom cholecystectomy was performed in Kobe Rosai Hospital with diagnosis of AC according to TG13. (1, 2) Between April 2010 and December 2015, a total of 77 consecutive patients who underwent cholecystectomy (52 laparoscopic, 25 open) were eligible for this study.

Comparison of surgical outcomes

Patients were classified into two groups. In one group EO was performed (n=38: EO group), and in the other PGD was performed. (n=39: PGD group) In order to evaluate the effectiveness of PGD on surgery, surgical results (operation time, blood loss, conversion rate, complication rate of LC and postoperative hospital stay) were compared between the PGD group and the EO group for AC.

Next, according to the period from drainage to operation, the patients who underwent PGD were classified into two groups. One was the group in which early surgery was undergone within 14 days from drainage to surgery (≤ 14 days: PGD-E) and the other experienced delayed surgery performed after more than 15 days had passed (> 14 days: PGD-D). Next surgical results (operation time, blood loss, conversion rate, complication rate, postoperative hospital stay and total hospital stay) were compared between the two groups. In accordance with previous reports, we decided on 14 days as the cut off value for the period from drainage to surgery. (14,15)

Moreover in the laparoscopic cholecystectomy (LC) group (n=52), surgical results (conversion rate to open in addition to the above) were also compared between PGD (n=24) and EO (n=28), and between PGD-E (n=10) and PGD-D (n=14). Furthermore, in patients taking anticoagulant drugs (n=30), surgical results were compared between the EO group (n=19) and the PGD group (n=11).

Preoperative gallbladder drainage (PGD)

Percutaneous transhepatic gallbladder aspiration (PTGBA or PTGBD) were performed for patients who could not undergo surgery because of high risk conditions of the patient, severity of AC or the hospital situation. The selection of either PTGBA or PTGBD was left to the judgment of the gastrointestinal physician. As a general rule, we waited until inflammation decreased after PGD and performed a delayed operation. However, when inflammation had not subsided sufficiently after PGD, we performed the operation as soon as possible.

Operative strategy and technique

In principle we perform LC for all benign diseases of gallbladder including AC. Although for high risk patients such as those complicated by respiratory disease as well as patients whose cystic duct could not be identified in

the preoperative imaging studies or patients with a history of surgery of upper abdomen in the past, open cholecystectomy (OC) was performed according to the judgment of the attending surgeon. LC was conducted by the standard four-port method. At Calot's triangle, the cystic duct and cystic artery were clearly shown in the critical view of safety and exfoliated after clipping. Next gallbladder was dissected from gallbladder bed. OC was also performed in a standard way by median, trans rectal or subcostal incision within 10 cm depending on the situation. At first the cystic duct and cystic artery were processed at Calot's triangle, and next the gallbladder was exfoliated from fundus to neck in the retrograde way. For cases in which bile was ruptured from the gallbladder during operation, the drain was indwelled.

Statistical analysis

Statistical analysis was performed using Stat MateV(ATMS Inc, Tokyo, Japan). Surgical results were analyzed using Student's t-test, chi-square test or Fisher's exact test. $P < 0.05$ was considered as statistically significant.

Ethical approval

This study was approved by the Ethics Committee of Kobe Rosai Hospital (approved No 29-04).

RESULTS

Clinical characteristics of all patients (PGD group $n=39$ and EO group: $n=38$) are shown in *table 1*. Moderate grade was most often the severity classification of cholecystitis, with 89.7% (35/39) in PGD and 89.5% (34/38) in EO. For methods of PGD, the numbers of PTGBD ($n=20$) and PTGBA ($n=19$) were similar. With regard to the timing of the operation after PGD the number of delayed surgeries ($n=22$) was more than early surgeries ($n=17$) (22:17). The enforcement rate of LC was 61.5% (24/39) in PGD and 68.4% (26/38) in EO. The number of patients taking anticoagulant drugs was 30 and its ratio was 39% (30/77); with 11 patients in PGD and 19 patients in EO.

Comparison of surgical outcomes between PGD and EO group is also shown in *table 1*. In the PGD group, blood loss was significantly less, (159.7/354.3, $p=0.022$) and operation time was significantly prolonged (180.9/154.8, $p=0.02$) compared to the EO group. There were no significant differences in the other factors.

In LC, blood loss of the PGD group was significantly

Table 1 - Comparison of clinical characteristic and surgical results between PGD and EO

	PGD (n=39)	EO (n=38)	p
Age	76 (59-91)	74 (43-91)	0.301
Gender			
Male	21	24	0.463
Female	18	14	
The grade of severity			
High	4	1	0.091
Moderate	35	34	
Low	0	3	
Operative procedure			
LC	24	28	0.422
OC	15	10	
Anticoagulant drugs use			
Yes	11	19	0.039
No	28	19	
Operation time (min)	180.9 (60-292)	150.7 (75-266)	0.014
Blood loss (ml)	159.7 (1-730)	354.3 (1-1476)	0.028
Postoperative hospital stay (day)	14.3 (4-38)	12.4 (4-65)	0.372
Postoperative complication rate (%)	5/39 (12.8)	4/37 (10.8)	0.506

PGD: preoperative gallbladder drainage group EO: emergency operation group

less (82.4/261.8, $p=0.009$) than that of EO, however operation time was not significantly different. (*table 2*)

In *table 3* clinical outcomes are compared between the PGD-E group and the PGD-D group. The mean period of early surgery from drainage to operation was 7.9 days, and the range was 3-14 days. Total hospital stay of PGD-E was significantly shorter than that of PGD-D. (29/40.8, $p=0.041$) However there were no significant differences in other factors. In the PGD-E group, we estimated whether there was a correlation between operation time and days from PGD to surgery (days), and between blood loss and days. There were no correlations between operation time and days (correlation coefficient : r^2 was 0.0665), or between blood loss and days (r^2 was 0.0346). (*fig. 1 a,b*)

When considering LC patients only, the mean period of early surgery from drainage to operation was 7.6 days. Total hospital stay of the PGD-E group was also significantly shorter compared with PGD-D. (22.3/34.9, $p=0.042$) However there were no significant differences in other factors. (*table 4*)

In *table 5* surgical results of patients taking anti-coagulant drugs were compared between the PGD and EO groups. In the PGD group, blood loss was significantly less (144.1/283.1, $p=0.045$) compared to the EO group and the operation time tended to be prolonged (181.7/147.8, $p=0.057$). In other factors there were no differences between the two groups.

Table 2 - Comparison of surgical outcome between PGD and EO in

	PGD (n=24)	EO (n=28)	p
Operation time (min)	174.8 (76-258)	157.1 (86-266)	0.104
Blood loss (ml)	82.4 (1-350)	261.8 (1-1175)	0.009
Postoperative hospital stay (day)	10.2 (4-25)	11 (4-65)	0.379
Conversion rate to open (%)	3/24 (12.5%)	4/26 (15.4%)	0.851
Postoperative complication rate (%)	1/24 (4%)	1/26 (3.8%)	0.954

Table 3 Comparison of surgical outcome according to the timing of operation after PGD

	PGD-E (n=17)	PGD-D (n=22)	p
The period from drainage to surgery (day)	7.9 (2-14)	35.8 (16-80)	<0.01
Operation time (min)	174.7 (91-260)	185.6 (60-292)	0.286
Blood loss (ml)	168.3 (1-730)	153 (1-600)	0.399
Postoperative hospital stay (day)	14.9 (7-30)	13.9 (4-38)	0.35
Postoperative complication rate (%)	3/17 (17.6)	2/22 (9.1)	0.428
Total hospital stay day)	29 (11-46)	40.8 (15-89)	0.041

Table 4 - Comparison of surgical outcome of PGD in LC

	PGD-E (n=10)	PGD-D (n=14)	p
The period from drainage to surgery (day)	7.6 (2-14)	34.2 (21-69)	<0.0
Operation time (min)	170.2 (91-258)	178 (76-231)	0.368
Blood loss (ml)	91.7 (1-327)	75.8 (1-350)	0.363
Postoperative hospital stay (day)	9.6 (7-13)	10.9 (4-25)	0.283
Conversion rate to open surgery (%)	1/10 (10)	2/14 (14.3)	0.753
Postoperative complication rate (%)	1/10 (10)	0/14 (0)	0.23
Total hospital stay (day)	22.3 (10-33)	34.9 (15-89)	0.042

Table 5 - Comparison of surgical outcome of cases with anticoagulant drugs between PGD and EO

	PGD (n=11)	EO (n=19)	p
Operation time (min)	181.7 (60-260)	147.8 (86-224)	0.057
Blood loss (ml)	144.1 (9-403)	283.1 (1-1476)	0.045
Postoperative hospital stay (day)	15.8 (8-35)	13.8 (3-65)	0.335
Conversion rate to laparotomy (%)	1/7 (14.3)	3/14 (21.4)	0.697
Postoperative complication rate (%)	3/11 (27.3)	2/19 (10.5)	0.234

Figure 1 - a, b - Correlation between operation time and days from PGD to surgery (days), $R^2 = 0.06654$ (a) and between blood loss and days, $R^2=0.03461$ (b)

DISCUSSION

Although we principally perform EO within 72–96 hours from onset of AC, in actuality there are occasions in which we do not perform EO for various reasons. In such cases, PGD is performed as the initial treatment and surgery follows. Recently in our hospital, after about one week had passed from the onset of AC, surgery was often undergone because inflammation had not improved sufficiently even after PGD. When we performed surgery with this timing for AC, we have seen the results and recognized that there were not such different surgical outcomes (operation time and amount of bleeding) compared to delayed surgery performed after inflammation has subsided.

In this study, when the surgical outcomes were compared between early surgery (≤ 14 days) and delayed surgery (> 14 days) after PGD, only in total hospital stay there was a significant difference. There were no significant differences in regard to operation time, blood loss, postoperative hospital stay, and postoperative complications. In LC similar outcomes were observed in that there were no significant differences between early and delayed surgery including conversion rate to open surgery. There was a tendency for blood loss in LC to be less than that in OC. The amount of bleeding might be reduced due to LC for AC. This result may be one of the reasons that LC for AC is recommended in TG13.

The advantages of delayed surgery for AC are to perform surgery easily and safely after inflammation has improved by waiting until the general condition of the seriously ill patients has improved. (15, 20) Previous reports suggest that the timing of surgery is made after considering the patient's condition, the hospital facilities available, and surgeons' experience based on the same outcomes as ours in which there were no differences between early and delayed surgery after PGD. (18) However if there is no difference in surgical outcomes, we would like to emphasize that early surgery might be recommended in comparison with delayed surgery, except for patients with unstable general conditions. Delayed surgery can lead to problems that lower the quality of life, especially in patients with PTGBD, including the extension of disease duration and hospital stay, an increase in cost and the risk of recurrence. (17) Moreover based on the result that there was little correlation between operation time, blood loss and days from PGD to surgery in the PGD-E group (≤ 14 days), it might be suggested that there was almost no difference in surgical outcomes even if surgery was performed at any time within 14

days after PGD. Therefore surgery could be performed safely and effectively for patients with PGD on any day within 14 days after PGD. Several authors have also described the advantages of performing surgery as early as possible from the onset of AC, which might lead to the reduction of total hospital stay, hospital charges and episodes of illness. (6,11,13,14, 21)

In the present study we compared the surgical outcomes between the PGD group and the EO group in order to evaluate the effect of PGD on surgery. Interestingly the data in the PGD group showed that blood loss was significantly reduced and operation time was significantly extended compared to the EO group. There were no significant differences in other factors. In surgery for AC an increase of the amount of bleeding has been a serious problem. These data suggested that PGD might be effective to reduce blood loss during surgery in some cases.

In regard to gallbladder drainage for AC, PTGBD was mainstreamed previously, and there were reports of its supremacy compared to PTGBA. (24, 25, 26) However, recently the usefulness of PTGBA has been reported. (27,28,29) Previously in our hospital PTGBD were performed in principle for AC. In fact the effect of drainage of PTGBD is superior to that of PTGBA. However there is a problem associated with PTGBD in that prolonged hospital stays and the lowering of quality of life because of tube troubles. (2) On the other hand, PTGBA is less invasive compared with PTGBD and is a treatment that can be carried out even at the bedside with an ultrasonography. Therefore recently PTGBA are preferentially performed in our hospital. However it is often necessary to repeat PTGBA in contrast to PTGBD. (28) Since PTGBD and PTGBA each has advantages and disadvantages, it is important to perform them selectively depending on the general condition of the patient. (29) If early surgery is scheduled after PGD, the drainage method might encounter no problems with PTGBA.

In this study the mean period from drainage to early surgery was 7.9 days. This corresponds to the so-called subacute phase. (22, 23) Problematic surgery during the subacute phase of AC had previously been considered to be difficult (22) because of thickening of the connective tissue or lack of recognition of Calot's triangle. Early surgery which we put forward occurs exactly during this subacute phase, and there are few reports (14) which recommend early surgery because of surgical difficulties in the subacute phase. However recently we have been able to perform surgery safely due to the evolution of devices, such as ultrasonically activated coagulating shears or vessel sealing systems, the progress of skills

and the standardization of safe surgeries in the critical view of safety. In general cholecystectomy is carried out by less experienced physicians as training, and that should be recommended. However it is considered to be important that especially in cases of subacute cholecystitis, experienced surgeons should perform cholecystectomy. (2)

Recently the number of patients taking anti-coagulant drugs has increased with 30 such patients out of 77 (39%) observed in the present study. It is difficult to perform PTGBD on these patients because of concern about bleeding due to damage to the liver in PTGBD. Thus in our hospital for these patients, recently PTGBA is preferentially selected as the first choice on the premise of surgery, and surgery was performed after the blood concentration of anticoagulant had decreased. The data for this study showed that in patients taking anti-coagulant drugs, there was a tendency for blood loss in the PGD group to be less than that of the EO group. Therefore for patients taking anticoagulant drugs, PGD was useful to reduce blood loss in surgery. This is because blood concentration of anticoagulant drugs might be decreased due to the interval which was brought about by PGD.

This study has several limitations. Because this study was retrospective and there were small patient numbers, especially for LC. Moreover it was the problem that the surgical outcomes of OC and LC were mixed. However it was considered that the tendency of the surgical results in this study would be unchanged even if the number of LC increased. Anyway a large-scale randomized control trial will be needed to clarify the optimal timing of surgery after PGD.

CONCLUSION

In conclusion, based on the current study, our strategy for AC is principally to conduct early surgery as soon as possible within 72~96 hours from the onset according to TG13. Even if PGD was carried out because emergency surgery could not be performed for some reason, early surgery should be performed as soon as possible after the system is in place. On the other hand, it should be considered that PGD be performed in cases of patients taking anticoagulant drugs in addition to cases of patients with a severe grade of AC and high risk factors.

Conflicts of interest

There is no conflicts of interest.

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