Evaluation of early cholecystectomy for acute cholecystitis within 10 days of onset, with arguments based on histopathological findings

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Research article

Abstract

Background: Histopathological findings would impact the timing of early cholecystectomy, but no reports have yet discussed. The aim of this study is to examine the feasible timing for early cholecystectomy based on both conventional clinicopathological data and histopathological findings.

Methods: We retrospectively analyzed 127 patients who underwent laparoscopic cholecystectomy for acute cholecystitis (AC) at in our institutes between 2010 and 2015. Patients were categorized into two groups according to the interval between surgery and symptom onset (early, £96 h; delayed, >96 h) for comparison of clinical results. In addition, both histopathological findings and clinical results were compared between the early group (£96 h) and a sub-delayed subgroup of patients who underwent cholecystectomy at >96 h but ≦240 h.

Results: No significant differences in surgical results were seen between the early group and delayed group. In terms of histopathological findings, the sub-delayed subgroup showed significant phase progression of cholecystitis compared to the early group. However, edema in the gallbladder (GB) wall was comparable in all cases operated on within 240 h, mirroring the lack of significant differences in surgical results seen between early and sub-delayed subgroups.

Conclusion: Edema in the GB wall with AC is continuous within 10 days from onset, and emergency laparoscopic cholecystectomy within this period is safe and feasible.

Background

Delayed laparoscopic cholecystitis (LC) was preferred for AC in the past, out of fear higher complication rate because of increased local inflammation and difficulty in dissection of Calot's triangle [1]. Several recent trials of early cholecystectomy have shown improved surgical results in parameters such as operation time, amount of bleeding, and conversion rate compared with delayed interval cholecystectomy [2-4]. The Japanese clinical guidelines for treating AC, proposed in 2005, provide criteria not only for diagnosis, but also for management depending on disease severity [5]. After the Japanese version, the Tokyo Guidelines 17 (TG07) were reported in 2007 as the first international practical guidelines [6]. Based on these guidelines, management of AC has been changed in many hospitals, including protocols for early surgery [7]. In the Japanese guidelines in 2005, early surgery is defined as operation within 96 h after symptom onset [5]. Thereafter, early surgery was defined within 72 h after symptom onset based on Tokyo guidelines (TG)13 [8], and other large studies favoring early cholecystectomy have recommended surgery within 48-72 h of admission [2-4]. However, those reports did not perform assessments based on the duration from symptom onset, and patients who underwent the operation >96 h after the development of AC but within 72 h of admission would thus still have been included in the "early" group.

AC develops from edematous cholecystitis through to necrotizing cholecystitis and finally suppurative/subacute cholecystitis over the course of about 10 days. These stages of cholecystitis can be confirmed from histopathological findings [9,10]. If the duration since onset of cholecystitis is

important for the indication of early cholecystectomy, histopathological findings would impact the timing of early cholecystectomy. However, no reports have yet discussed the timing of cholecystectomy in association with histopathological findings. For example, while edema in the gallbladder (GB) wall is associated with the ease of dissection [5], previous reports have not clarified the time course of such edema. The present study therefore examined the feasible timing for early cholecystectomy based on both conventional clinicopathological data and histopathological findings.

Methods

A retrospective analysis was carried out among patients who underwent laparoscopic cholecystectomy for AC at Steel Memorial Muroran Hospital between April 2010 and November 2015. Diagnosis and assessment of severity (severe, moderate or mild) were made according to the Japanese clinical guidelines for treating AC at that time [5].

Patients who had coexisting common bile duct stones or severe comorbidities, or who were receiving anticoagulant agents were excluded from the indication for early cholecystectomy. In principle, cholecystectomy was performed laparoscopically regardless of whether the operation was early or delayed. Laparoscopic cholecystectomy for AC was performed in 127 patients during the study period. All 127 cholecystectomy procedures were performed by experienced surgeons using the four-port method. A case of difficult laparoscopic surgery (CDLS) was defined as any case with operation time ³3 h and/or bleeding volume ³300 ml. First, patients were divided into two groups and compared based on performance of surgery about a cutoff of 96 h from symptom onset, according to the definition of early surgery in the Japanese clinical guidelines for treating AC at that time [5]. The early group comprised 52 patients who underwent surgery £96 h after symptom onset, while the delayed group comprised 75 patients who underwent surgery >96 h after symptom onset. Next, 10 patients who underwent cholecystectomy >96 h but £240 h after symptom onset were extracted from the delayed group as a sub-delayed subgroup and compared to the early group in terms of both histopathological findings and clinical results.

The 62 patients in the early and sub-delayed subgroups (i.e., patients who underwent cholecystectomy £240 h) were divided by histopathological findings into three sequential phases according to the classification published by Muto et al. [9]: edematous cholecystitis; necrotizing cholecystitis; and suppurative/subacute cholecystitis. Moreover, edematous status of the GB wall was assessed in these cases as an indicator of the ease of dissection. An experienced pathologist confirmed the histopathological features of all cases.

Finally, the 62 patients in the early and sub-delayed subgroups were divided into the 6 subgroups based on performance of surgery about cutoffs of 24 h, 48 h and 72 h from symptom onset for comparison of clinical results in ultra-early stages. Group 1 comprised patients who underwent cholecystectomy at £24 h, Group 2 at >24 h but £240 h, Group 3 at £48 h, Group 4 at >48 h but £240 h, Group 5 at £72 h, and

Group 6 at >72 h but £240 h. Group 1 was compared to Group 2, Group 3 to Group 4, and Group 5 to Group 6.

Statistical analysis

Statflex version 6 software (Artech Co.,Ltd., Osaka, Japan) was used for all statistical analyses. The c^2 and Fisher's exact test were employed for categorical variables, and Student's t test was used for continuous variables. Values of $p<0.05$ were considered statistically significant. Multiple comparisons were performed with the Tukey-Kramer test.

Results

Characteristics of the 127 participants are shown in Table 1. Median age at the time of surgery was 63 years (range, 23–88 years), and 33.9% of all patients were women. AC was severe in 16 patients, moderate in 69, and mild in 42. Of the127 cases, CDLS and/or conversion cases were encountered in a total of 21 patients (16.5%). Postoperative complications were seen in 9 cases (7.1%). Median hospital stay was 10.5 days (range, 4–85 days).

With respect to the interval between surgery and onset of AC symptoms, based on the 96-h cutoff, Table 2 shows a comparison of various characteristics between the early and delayed groups. No significant differences were seen between each group in terms of median age (62.5 years vs. 66 years, respectively; p = 0.388), sex ratio, distribution of severity, median operation time (106.5 min vs. 123 min, respectively; p = 0.668), median bleeding (7 ml each; p = 0.739), CDLS and/or conversion rate (19.2% vs. 14.7%, respectively; p = 0.496), or postoperative complication rate (7.7% vs. 6.7%, respectively; p = 0.544). However, the early group showed a significantly shorter total hospital stay (7 days vs. 19 days, respectively; p < 0.001), as previously reported (Table 3) [11].

Table 3 shows a comparison of characteristics between early and sub-delayed groups. No significant differences between early and sub-delayed subgroups were seen in terms of median age (62.5 years vs.60 years, respectively; p = 0.196), sex ratio, or distribution of severity. In addition, no significant differences were seen between the two groups in terms of surgical results such as operation time (106.5 min vs. 115.5 min, respectively; p = 0.521), bleeding volume (7 ml vs. 13.5 ml, respectively; p = 0.090), CDLS and/or conversion rate (19.2% vs. 10%, respectively; p = 0.430or postoperative complication rate (7.7 vs. 10 respectively; p = 0.598), although total hospital stay was significantly shorter in the early group (7 days) than in the sub-delayed subgroup (11 days; p = 0.005).

Furthermore, the 62 patients in the early and sub-delayed subgroups were classified according to histopathological findings (Table 4), with edematous cholecystitis in 11 cases (17.7%), necrotizing cholecystitis in 38 (61.3%), and suppurative/subacute cholecystitis in 13 (21.0%). The median interval between symptom onset and cholecystectomy was 2 days (range, 1–4 days) in cases with edematous cholecystitis, 3 days (range, 1–7 days) with necrotizing cholecystitis, and 6.5 days (range, 5–9 days) with suppurative/subacute cholecystitis. Significant differences in the phase of cholecystitis were seen

between the early and sub-delayed subgroups. In the early group, 44 of 54 patients (84.6%) showed edematous cholecystitis or necrotizing cholecystitis, representing the early stages of AC, whereas 5 of the 5 patients (50%) in the sub-delayed subgroup patients showed suppurative/subacute cholecystitis (Table 3). However, edema in the GB wall remained at the same level in all cases operated on within 240 h after symptom onset.

Surgical results for each type of cholecystitis are listed in Table 4. Edematous cholecystitis showed the most favorable outcome in the three sequential histological phases, with shorter operation time (82 min vs. 126.5 min and 115.5 min; p = 0.013 and p = 0.333) and less bleeding (5 ml vs. 7 ml and 13.5 ml; p = 0.059 and p = 0.076) compared to the other two histopathological groups (Table 4). On the other hand, necrotizing cholecystitis was associated with even longer operation time (126.5 min) than suppurative/subacute cholecystitis (115.5 min, p = 0.098) and the CDLS and/or conversion rate was 23.7%, representing the worst rate for the three histopathological phases (Table 4).

Table 5 shows a comparison of various characteristics in ultra-early stages about cutoffs of 24 h, 48 h and 72 h from symptom onset. No significant differences were seen between each group in terms of surgical results such as operation time, bleeding volume, CDLS and/or conversion rate, or postoperative complication rate, or total hospital stay.

Discussion

The Japanese clinical guidelines for treating AC was proposed in 2005 [5] and an international consensus for treating AC was published as the Tokyo Guidelines in 2007[6]. The guidelines describe the timing and optimal surgical treatment of AC in a question-and-answer format. At the Tokyo meeting, early cholecystectomy (until 96 h after symptom onset) and LC were preferred to late and open cholecystectomy [12]. Thereafter, early cholecystectomy was defined until 72 h after symptom onset [8].

Several studies have supported the superiority of early cholecystectomy in terms of total hospital stay, and no significant differences in conversion or complication rates have been found between early and late groups [2, 13]. Our study also confirmed the advantage of operation < 96 h after symptom onset over later operation.

In the Tokyo Guidelines, early surgery was defined as occurring < 96 h after AC onset [, 8]. The underlying theory is that dissection is made markedly easier by the edematous changes present in the GB wall, and many reports support this theory [4, 5]. However, in reality, no reports have actually clarified how long these edematous changes last. Moreover, patients with AC do not necessarily present to a hospital where surgery can be performed as soon as symptoms arise, as in our data [14]. Nevertheless, two important randomized studies evaluated the timing of early surgery on the basis of the time from admission, rather than from the onset of symptoms [3, 4]. Therefore, there is room for discussion about the time limitations for early surgery. The present study analyzed the feasibility of cholecystectomy within 10 days after symptom onset. The reason is that development of AC is reported within about 10 days, with subsequent progression to chronic cholecystitis [5, 9]. Within the acute stage of those 10 days, AC progresses from

edematous cholecystitis through necrotizing cholecystitis to suppurative/subacute cholecystitis. Our histopathological findings confirmed that AC proceeds in this order (Table III). Moreover, we revealed that edema in the GB wall, an indicator of the ease of dissection, remains consistently present for around 10 days; in our data, no differences in surgical parameters such as operation time, bleeding volume or postoperative complication rate were seen between early and sub-delayed subgroups, which seemed to reflect the lasting edema in the GB wall.

Some reports describe similar findings to ours. Low et al. recommended urgent LC from 72 h to 2 weeks after admission, while Popkharitov et al. reported that LC performed 4–7 days after symptom onset is not inferior to earlier LC in terms of surgical outcomes [15, 16].

On the other hand, some differences were seen with regard to clinical results for each histopathological type. Edematous cholecystitis represents the most suitable phase for early cholecystectomy within 10 days after AC onset, while patients with necrotizing cholecystitis and suppurative/subacute cholecystitis underwent a longer operation and experienced comparatively more bleeding.

However, edematous cholecystitis occurs at the beginning of the AC and rapidly develops to necrotizing cholecystitis [9]. As a result, relatively few patients present to a hospital and undergo cholecystectomy while edematous cholecystitis remains. In the present study, edematous cholecystitis was only seen in 16.7% of cases operated on within 10 days. Clearly, other reports preferring early cholecystectomy dealt with not only edematous cholecystitis, but also necrotizing, suppurative/subacute cholecystitis.

We also compared the surgical results among patients who underwent cholecystectomy in the ultra-early stages from symptom onset, to clarify the impact of performing surgery during the stage of edematous cholecystitis. Unexpectedly, no differences in surgical results were seen between these time periods (Table V). The reason may be that necrotizing cholecystitis, which was associated with the worst operative results among the three phases of AC according to our data, rapidly develops from edematous cholecystitis, and would worsen surgical results in the ultra-early stage.

Older patients (over 75 years) have recently been excluded from the indications for early cholecystectomy in our hospital. In principle, older patients should be operated on after careful evaluation of preoperative physical status, because recent evidence demonstrates nearly 10-fold higher mortality rates among elderly individuals undergoing major surgery compared to younger patients [17]. Percutaneous transhepatic gallbladder drainage (PTGBD) may thus be preferable for older patients with AC [18].

Finally, the feasibility of urgent cholecystectomy beyond 11 days after symptom onset remains unclear. We agree with the point that there is a worse timing for cholecystectomy during the process of changing from AC to chronic cholecystitis [19]. In the future, clarification of the cutoff for delayed interval cholecystectomy is required. Moreover, according to the updated Tokyo Guidelines 2013 [37], the treatment for AC in our institute will be influenced to a certain degree for the future.

Conclusions

In conclusion, this is the first report to examine feasible operative timing for AC based on histopathological findings. We revealed that edema in the GB wall continues for around 10 days after the onset of symptoms of AC, so emergency cholecystectomy in this period is safe and feasible. Even if 5–10 days has passed since symptom onset, early surgery offers both medical and socioeconomic benefits compared with delayed interval surgery.

Abbreviations

ALT: alanine///; AST: AC: acute cholecystitis; GB: gallbladder; LC: laparoscopic cholecystitis; CDLS: case of difficult laparoscopic surgery; PTGBD: percutaneous transhepatic gallbladder drainage

Declarations

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Author contribution

S H and N S designed the research; S H, M F and S Hi analyzed the data; S H wrote the paper.

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Availability of data and materials

The datasheets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The institutional review board of Steal Memorial Muroran Hospital (Muroran, Japan) waived the need for informed consent because this was a retrospective study.

Consent for publocation

Not applicable

Competing interests

Satoshi Hayama and other co-authors declare that there is no conflict of interest.

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Tables

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