

Outcome of Delayed Cholecystectomy after Percutaneous Cholecystostomy for Acute Cholecystitis

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ABSTRACT: **Background:** Recent studies have suggested that urgent cholecystectomy is the preferred treatment for acute cholecystitis. However, initial conservative treatment followed by delayed elective surgery is still common practice in many medical centers.

Objectives: To determine the effect of percutaneous cholecystostomy on surgical outcome in patients undergoing delayed elective cholecystectomy.

Methods: We conducted a retrospective analysis of all patients admitted to our medical center with acute cholecystitis who were treated by conservative treatment followed by delayed cholecystectomy between 2004 and 2013. Logistic regression was calculated to assess the association of percutaneous cholecystostomy with patient characteristics, planned surgical procedure, and the clinical and surgical outcomes.

Results: We identified 370 patients. Of these, 134 patients (36%) underwent cholecystostomy during the conservative treatment period. Patients who underwent cholecystostomy were older and at higher risk for surgery. Laparoscopic cholecystectomy was offered to 92% of all patients, yet assignment to the open surgical approach was more common in the cholecystostomy group (16% vs. 3%). Cholecystostomy was associated with significantly higher conversion rates to open approach (26% vs. 13%) but was not associated with longer operative time, hemorrhage, surgical infections, or bile duct or organ injuries.

Conclusions: Treatment with cholecystostomy is associated with higher conversion rates but does not include other major operative-related complications or poorer clinical outcome.

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KEY WORDS: cholecystectomy, cholecystitis, cholecystostomy, cholelithiasis

For editorial see page 651

Acute cholecystitis (AC) is one of the most common urgent surgical conditions encountered in the Western world. Surgical management of patients with AC may be treated by means of laparoscopic or open cholecystectomy, or on a delayed

elective basis following the resolution of the acute inflammatory phase by conservative treatment. Although recent studies suggest that early surgical intervention is the preferred standard of treatment, many medical centers still prefer to first treat patients conservatively. In that situation, cholecystectomy is delayed for elective surgery [1-3]. This practice is especially common for elderly patients and those with serious medical comorbidities in whom emergency cholecystectomy is associated with high morbidity and mortality rates [4]. When conservative management is considered, treatment is commonly successful for most patients with antibiotics alone. However, in some patients, the use of percutaneous cholecystostomy (PC) may be needed to interrupt the natural progression of an ongoing and non-resolving inflammatory process. This measure has been found to be highly successful as a temporary bridging procedure before delayed surgery or as a definitive alternative treatment strategy in high-risk patients with severe underlying diseases who are considered unfit for surgery [5,6].

While numerous studies have described the general outcomes of patients treated by PC or the differences in outcomes in patients receiving cholecystostomy versus cholecystectomy, to the best of our knowledge, no population-based studies have compared surgical outcomes of delayed elective surgery in patients who received PC versus those who did not receive this care as part of the initial conservative treatment due to AC. Thus, the aim of the present study was to evaluate the effect of PC placement on surgical and clinical outcome of delayed elective cholecystectomy.

PATIENTS AND METHODS

PATIENTS

We performed a retrospective chart review of all patients admitted for treatment of AC at our medical center between 2004 and 2013. Patients were identified by ICD-9 diagnosis codes [Figure 1]. All patients included in the study had positive clinical signs and symptoms, laboratory tests, and sonographic findings compatible with the diagnosis of acute calculus cholecystitis [7-9]. Following diagnosis, conservative treatment that included intravenous administration of fluids, broad spectrum antibiot-

ics, and analgesics was immediately provided to all patients.

PC was performed at the interventional unit of the department of radiology. The gallbladder was localized with ultrasound and punctured under local anesthesia using a transhepatic approach if possible. A self-retaining pigtail catheter was placed in the gallbladder lumen and drained fluid was cultured. The decision to perform PC was based on the surgeon's perception of lack of response, or poor response, to treatment or due to associated co-morbidities. Similarly, the period of time the tube was left in place was at the discretion of the treating surgeon.

All patients were referred to delayed elective cholecystectomy. Clinical and surgical outcome parameters following surgery were compared between patients who underwent PC and those who did not (134 [36%] and 236 [64%] patients, respectively). Patients who did not undergo delayed cholecystectomy at our medical center or those patients who underwent urgent operations were excluded from the study.

STATISTICAL ANALYSIS

Categorical variables were presented as frequencies and percent. Continuous variables were presented as mean \pm standard deviation (median, range). The association between PC (yes/no) and the categorical variables was examined using the chi-square test or Fisher's exact test. For continuous variables, Student's *t*-test or Wilcoxon rank-sum test were used. Outcome variables, such as laparoscopy converted to open surgery, were also examined and univariate and multivariate logistic regression were performed. Odds ratio (OR) along with 95% confidence intervals (95%CI) were presented. Statistical significance was considered if $P < 0.05$. Statistical analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA)

RESULTS

Data were collected from the medical center's database for all ICD-9 codes of hospitalized patients presenting with bile stones from 2004 to 2013. We reviewed 1975 cases, of which 1399 were diagnosed with bile stone complications other than acute cholecystitis. Diagnoses included biliary colic, biliary pancreatitis, or obstructive jaundice [Figure 1]. In total, 576 patients were diagnosed with acute cholecystitis. Of these, 370 patients met the inclusion criteria of the study, and complete data were collected for all of these patients. In this cohort of patients, there were 168 female and 202 male patients with a mean age of 60 (range 37–77 years). According to the American Society of Anesthesiologists (ASA) score, 154 patients (41.62%) were defined as ASA I, 143 (38.65%) as ASA II, and 73 (19.73%) as ASA III and IV. Patient characteristics are summarized in Table 1.

From our cohort, 134 patients (36%) underwent PC tube insertion during the initial admission. Patients undergoing PC were significantly older (63.6 ± 13.5 years vs. 54.5 ± 17.5 years,

$P < 0.0001$) and at higher risk for surgery ($P < 0.0001$) [Table 1]. Of the PC group of patients, 30% were classified as ASA III and above, compared to only 13% in the non-PC group. Mean length of stay (LOS) of initial hospitalization was 6 days for patients treated without PC compared to 10 days in the PC group ($P < 0.0001$).

Following resolution of the acute disease, all patients were referred for delayed elective surgery. In total, 342 patients (92% of all study patients) were assigned to laparoscopic cholecystectomy [Table 2]; 28 patients were referred for the open surgical approach within the first 2 years of the study (2004–2006). Of these, 21 (75%) were patients who underwent PC during their initial admission. Assignment to the open surgical approach was significantly more common in the PC group of patients compared to non-PC treated patients (16% vs. 3%, respectively, $P < 0.0001$). Sub-analysis revealed that patients assigned to open cholecystectomy were older than 60 years of age and had an ASA classification of II or III.

Laparoscopic cholecystectomy was successfully completed in 282 patients (83%). Reported surgical time was not significantly different in the two groups (88.8 vs. 96.8 minutes,

Table 1. Association of clinical characteristics and initial admission length of stay in treated and untreated patients with percutaneous cholecystostomy

	Percutaneous cholecystostomy		P value
	No n=236	Yes n=134	
Age, years (median)	54.5 \pm 17.5 (56)	63.6 \pm 13.5 (65)	< 0.0001
Male	100 (42%)	68 (51%)	0.12
ASA 1	117 (50%)	37 (28%)	< 0.0001
ASA 2	87 (37%)	56 (42%)	
ASA 3+	32 (13%)	41 (30%)	
Initial admission LOS (median)	6.9 \pm 7.8 (6)	10.5 \pm 6.4 (10)	< 0.0001

$P < 0.05$ was considered statistically significant

Categorical variables are presented by percent. Continuous variables are presented by mean \pm standard deviation (median)

ASA = American Society of Anesthesiologists

Table 2. Association of clinical and surgical characteristics of patients untreated and treated with percutaneous cholecystostomy

	No n=236	Yes n=134	P value
Initial open approach	7 (3%)	21 (16%)	< 0.0001
Laparoscopy converted to open	31 (13%)	29 (26%)	0.0055
Operation time, minutes (median)	88.8 \pm 39.3 (81)	96.8 \pm 37.2 (90)	0.0766
LOS (median)	3.2 \pm 3.8 (2)	4.3 \pm 6.5 (2)	0.1139
Superficial SSI (%)	6 (2.5)	11 (8)	0.0123
Deep SSI (%)	6 (2.5)	7 (5)	0.2395
Death (%)	3 (1)	1 (0.7)	NS

LOS = length of stay (following surgery), NS = not significant, SSI = surgical site infection

$P = 0.0766$) [Table 2]. However, the conversion rate from laparoscopic to open approach was significantly higher in the PC-treated group of patients compared to patients treated with antibiotics alone (26% vs. 13%, respectively, $P = 0.005$) [Table 2]. Multivariate analysis was used to evaluate the association of different factors including PC insertion, age, gender, ASA classification, and the rate of conversion to open approach. Results showed that PC insertion was a significant and independent risk factor for conversion to open approach during delayed laparoscopic cholecystectomy ($P = 0.037$, OR 1.9, 95%CI 1.04–3.3) [Table 2]. Age was also found to be a significant risk factor for conversion. In univariate analysis, every 5 years of age contributed an OR of 1.2 to conversion (95%CI 1.1–1.3). A multivariate analysis confirmed that age is an independent risk factor for conversion with an OR of 1.1 for every 5 years of age ($P = 0.009$, 95%CI 1.04–1.2).

Postoperative surgical site infection (SSI) incidence was significantly higher in the PC-treated group of patients [Table 2]. Overall, superficial SSI was reported in 11 of 134 patients (8%) from the PC-treated group of patients compared to 6 of 236 patients (2.5%) treated without PC ($P = 0.0123$). However, we identified a clear association between open surgery and superficial SSI. Twelve out of 17 patients (70%) presenting with superficial SSI underwent surgery in an open approach, including two patients who underwent conversion from laparoscopic to the open approach. Thus, when surgery was successfully completed by laparoscopy (282 patients; 83% of all study patients), we found no differences in the incidence of superficial SSI between the PC treated and untreated patients [Table 3]. Superficial SSI was also related to the length of surgery. The mean surgical time was longer in patients presenting with SSI compared to the overall mean time of the study population (118 minutes vs. 88.8–96.8 minutes). Deep SSI rates were not significantly different in the two groups. Seven patients in the PC treatment group (5%) had deep SSI within 30 days of elective surgery, compared to six deep SSIs (2.5%) in the antibiotic treatment group ($P = 0.2395$) [Table 2]. Similarly, postoperative LOS was not significantly different in the two groups [Table 2].

Severe surgical complications were also not significantly different in the two groups of patients. One patient in the PC

group had small bowel injury identified during laparoscopy and underwent immediate bowel repair. In the non-PC treated group, one patient presented with a common bile duct injury that required endoscopic retrograde cholangiopancreatography and stenting. Another patient in this group presented with postoperative intra-abdominal hemorrhage, which required laparotomy.

Overall, four deaths were recorded. Three deaths were recorded in the PC group (1% of patients) [Table 2]. One patient presented with an intra-abdominal hemorrhage and hemorrhagic shock and died 3 days after laparotomy in the intensive care unit (ICU). Two patients died of sepsis and multiple organ failure in ICU. In the antibiotic treatment group, one death (0.7% of patients) was recorded after a rapid postoperative clinical deterioration, ICU admission, and septic shock.

DISCUSSION

Recent studies have provided evidence showing that early laparoscopic cholecystectomy is the treatment of choice for most patients presenting with acute cholecystitis [1-3,9-13]. However, earlier reports have shown that the mortality rates of urgent operations among elderly or critically ill patients with acute cholecystitis may be as high as 14–19% [8,14]. These rates were dramatically reduced to less than 2% in the same population of patients when surgery was deferred and performed electively [15,16].

Since elective surgery is safer than emergency surgery in high-risk patients, conservative treatment has been suggested as a bridging strategy during the acute phase of the disease. This latter approach was found to be highly successful; therefore, many medical centers have adopted this protocol for their patients as well [17]. However, in some patients, conservative therapy based on antibiotic treatment is insufficient and additional interventional assistance to prevent clinical deterioration may be required [18]. In these cases, ultrasound guided PC was found to be an attractive and useful way to treat severe inflammatory cases. The procedure, first described by Radder [12], is a safe, minimally invasive procedure with very low morbidity and mortality rates [19-22]. This modality was more commonly used as an alternative treatment for very high-risk patients who could not undergo cholecystectomy or in those with severe cholecystitis where definition of biliary anatomy was difficult to discern.

Recent studies have shown that PC placements in select populations, such as the elderly, may decrease morbidity, mortality, and the need for open operations [23-25]. In these studies, the most immediate complications of PC were minor while fatal complications were rare. However, despite the increasing use of PC, the indications for its placement in the setting of acute cholecystitis are not yet standardized. Treatment decisions are generally left to the discretion of the treating sur-

Table 3. Postoperative outcome in untreated and treated patients with PC that completed surgery by laparoscopy

	Percutaneous cholecystostomy		P value
	No (n=198)	Yes (n=84)	
LOS (median)	2.5 ± 2.9 (2)	2.4 ± 2.1 (2)	0.875
Superficial SSI (%)	2 (1)	3 (4)	0.1584
Deep SSI (%)	3 (1.5)	3 (4)	0.3672
Death (%)	0 (0)	1 (1)	0.2954

$P < 0.05$ was considered statistically significant
LOS = length of hospital stay, SSI = surgical site of infection

geons. Moreover, image-guided PC is increasingly being used as a bridge to delayed laparoscopic cholecystectomy, even in patients without severe co-morbidities or evidence for severe cholecystitis [23-25]. It is, therefore, important to determine whether the placement of PC inversely affects surgical outcome, and as such cautious should be used.

In the present study, we performed a retrospective analysis of the surgical outcome of delayed elective cholecystectomy in patients treated with PC (134 patients) compared with those treated without PC placement (236 patients). Patients treated with PC were more frequently assigned to open surgery compared to patients treated successfully without tube insertion. The decision to assign to open surgery was at the discretion of the surgeon. Although the reasons for this finding are not clear, we postulate that a possible explanation may be that the surgeons thought that surgery would be safer and easier using this approach, and they were less comfortable with the performance of laparoscopic surgery following a difficult conservative course. Indeed, we found that all of the referrals for open surgery were completed during the first 2 years of the study (2004-2006), whereas after this period all patients were assigned to laparoscopic cholecystectomy. Among patients undergoing laparoscopic surgery (92% of patients), treatment with PC was associated with a significant increase (26% vs. 13%) in the need for conversion to open approach to complete the surgical procedure. According to the operative notes of these cases, the conversions were attributed to operative difficulties resulting from severe local adhesions and secondary inflammatory responses. These difficulties were more commonly observed after tube drainage. It is important, however, to note that PC was not associated with increased operative time or with severe intra-operative complications such as bile duct injuries, organ injuries, or severe hemorrhage.

Superficial postoperative surgical site infections were significantly more common following tube placement. However, it should be noted that when surgery was completed by laparoscopy (83% of cases), there were no differences in the two groups of patients. Thus, the differences in the rate of superficial surgical site infections could probably be attributed to the increased incidence of open surgery in patients undergoing PC insertion rather than secondary infection due to tract colonization. This finding may be further augmented by the lack of differences in the rates of deep surgical site infections in the two groups regardless of surgical technique.

The results of this study strongly suggest that placement of PC increases the technical difficulty of surgery, leading to increased conversion rates and its associated complications, such as superficial surgical site infections. Although major complications were not associated with PC in our study, it can be assumed that they may occur more commonly due to the technical difficulties encountered during surgery. It may be that the lack of such complications, such as bile duct or organ inju-

ries, are the result of a rather low threshold policy of conversion to open approach in this series of patients.

The percentage of patients who underwent PC placement in this study is high, suggesting that the procedure was not performed strictly for patients with severe co-morbidities or technically challenging settings. Mortality rates were very low as were severe postoperative complications, including patients with high surgical risk.

CONCLUSIONS

Despite the overall findings in this study on the effect of PC insertion on surgery, there are negative effects of PC on laparoscopic surgical outcome. Moreover, it seems that the policy of initial conservative treatment is overused in many medical centers, especially in patients without increased surgical risk. This policy needs to be changed in light of studies showing high success rates with low morbidity and mortality rates as well as reduced costs when urgent surgical intervention is used.

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Capsule

National surveillance for *Clostridioides difficile* Infection, Sweden, 2009–2016

Rizzardi and co-authors reported results from a national surveillance program for *Clostridioides difficile* infection (CDI) in Sweden, where CDI incidence decreased by 22% and the proportion of multidrug-resistant isolates decreased by 80% in 2012–2016. Variation in incidence between counties also diminished during this period, which might be attributable to implementation of nucleic acid amplification testing as the primary diagnostic tool for most laboratories. In contrast to other studies, this study did not indicate increased CDI incidence attributable the introduction of nucleic acid ampli-

fication testing. These results also suggest that successful implementation of hygiene measures is the major cause of the observed incidence decrease. Despite substantial reductions in CDI incidence and prevalence of multidrug-resistant isolates, Sweden still has one of the highest CDI incidence levels in Europe. This finding is unexpected and warrants further investigation, given that Sweden has among the lowest levels of antimicrobial drug use.

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Capsule

Reversing autoimmunity combination of rituximab and intravenous immunoglobulin

In this concept paper, **Ahmed and Kaveri** presented a unique and novel protocol to treating autoimmune diseases that may have the potential to reverse autoimmunity. This protocol uses a combination of B cell depletion therapy (BDT), specifically rituximab and intravenous immunoglobulin (IVIg), based on a specifically designed protocol (Ahmed Protocol). Twelve infusions of rituximab are given in 6–14 months. After the CD20+ B cells are depleted from the peripheral blood, IVIg is given monthly until B cells repopulation occurs. Six additional cycles are given until the end of the protocol. During the stages of B cell depletion, repopulation, and after clinical recovery, IVIg is continued. Along with clinical recovery, significant reduction and eventual disappearance of pathogenic autoantibodies occurs. Administration of IVIg in the post-clinical period is a crucial part of this protocol. This combination reduces, and may eventually significantly eliminate, inflammation in the microenvironment and facilitate restoring immune

balance. Consequently, the processes of autoimmunity and the phenomenon that lead to autoimmune disease are arrested, and a sustained and prolonged disease and drug-free remission is achieved. Data from seven published studies in which this combination protocol was used are presented. BDT does not affect check points. IVIg has functions that mimic checkpoints. Hence, when inflammation is reduced and the microenvironment is favorable, IVIg may restore tolerance. The authors provide relevant information, molecular mechanism of action of BDT, IVIg, autoimmunity, and autoimmune diseases. The focus of the manuscript describes possible pathways used by the combination of BDT and IVIg in providing sustained, long-term, drug-free remissions of autoimmune diseases, and thus reversing autoimmunity, albeit for the duration of the observation.

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