ORIGINAL ARTICLE

The Treatment of Critically Ill Patients With Acute Cholecystitis

A Systematic Review and Meta-analysis Comparing Percutaneous Cholecystostomy and Cholecystectomy

Peter C. Ambe, Sarantos Kaptanis, Marios Papadakis, Sebastian A. Weber, Stefan Jansen, Hubert Zirngibl

SUMMARY

Background: Besides cholecystectomy (CC), percutaneous cholecystostomy (PC) has been recommended for the management of critically ill patients with acute cholecystitis. However, solid evidence on the benefit of PC in this subgroup of patients is lacking.

Methods: In accordance with the PRISMA guidelines for systematic reviews, we systematically searched the Cochrane Library, CINAHL, MEDLINE, Embase, and Scopus for relevant studies published between 2000 and 2014. Two investigators independently screened the studies included.

Results: Six studies with a total of 337 500 patients (PC 10 045, CC 327 455) were included for meta-analysis. Significant differences in favor of CC were recorded with regard to the rate of mortality (OR 4.28, [1.72 to 10.62], $p = 0.0017$), length of hospital stay (OR 1.41, [1.02 to 1.95], $p = 0.04$), and the rate of readmission for biliary complaints (OR 2.16, [1.72 to 2.73], $p < 0.0001$). There was no statistically significant difference between both intervention arms with regard to complications (OR 0.74, [0.36 to 1.53], $p = 0.42$) and re-interventions (OR 7.69, [0.68 to 87.33], $p = 0.10$).

Conclusion: The benefit of percutaneous cholecystostomy (PC) over cholecystectomy (CC) in the management of critically ill patients with acute cholecystitis could not be proven in this systematic review.

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Acute cholecystitis (AC) is a common and potentially life-threatening condition. While early cholecystectomy (surgical removal of the gallbladder independent of the means of access) has been unequivocally established as the gold standard for the management of young and “fit for surgery” patients with AC (1–3), the optimal management of critically ill and elderly patients with acute cholecystitis remains a topic of discussion. The surgical management of elderly and critically ill patients is thought to be associated with poor outcomes. Rates of morbidity and mortality as high as 40% and 13% respectively have been reported in this critical subset of patients (4–7).

Current guidelines, including the well established Tokyo guidelines recommend gallbladder drainage via percutaneous cholecystostomy (placement of a drain or a tube with the aim of draining the gallbladder content usually performed under local anesthesia and image guidance via ultrasound or computed tomography) in such cases (8, 9). The number of publications on percutaneous cholecystostomy (PC) rapidly increased after the publication of the Tokyo guidelines. Many authors have either used PC as a bridge to surgery or as a definitive management of AC. These publications however are entirely retrospective with limited case numbers (10–12). Therefore, no solid evidence on the benefit of PC has been established in the medical literature so far. The aim of this systematic review therefore was to investigate the clinical benefit of PC in the management of critically ill patients with acute cholecystitis by comparing the outcomes of critically ill patients managed with PC to those of similar patients managed with cholecystectomy (CC). The null hypothesis assumed there is no difference amongst both interventions with regard to outcomes.

Methods

The study was designed in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (13). A protocol with methodological details was published previously (14).

Department of General and Visceral Surgery, HELIOS University Hospital Wuppertal, Universität Witten-Herdecke: Dr. med. Ambe, Dr. med. Papadakis, Herr Jansen, Prof. Dr. med. Zirngibl
Homerton University Hospital, Queen Mary, University of London, Großbritannien: Dr. Kaptanis MSc, MRCS(Glasg), FHEA

Department of Internal Medicine, St. Elisabeth Krankenhaus Köln-Hohenlind: Dr. med. Weber

TABLE

Characteristics of studies included*

Reference	Number of patients	Study design	Newcastle–Ottawa Scale	Mortality rate	Complication rate	Re-intervention rate	Length of stay	Readmission rate
(20)	42	Prospective study	6	Yes	Yes	Yes	Yes	Yes
(17)	201	Retrospective study	8	Yes	Yes	Yes	Yes	No
(21)	61	Prospective study	7	Yes	Yes	Yes	Yes	Yes
(22)	1725	Case–control study	7	Yes	Yes	No	Yes	Yes
(18)	306 747	Multicenter outcome study	8	Yes	Yes	No	Yes	No
(19)	43 341	Longitudinal analysis	7	Yes	No	No	Yes	No

* Studies published between 2000 and 2014 were included

Literature search

A systematic search of the Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL), MEDLINE, Embase and Scopus was performed. We used the following search terms: acute cholecystitis OR severe cholecystitis OR cholecystitis AND cholecystectomy OR laparoscopic cholecystectomy OR open cholecystectomy AND Cholecystostomy OR percutaneous cholecystectomy OR gallbladder drain OR gallbladder tube OR transhepatic gallbladder drain OR transhepatic gallbladder tube OR cholecystostomy tube. The search was limited to original articles based on human studies published between 2000 and 2014. In addition the “related citation” function in PubMed was used to widen the search. Finally, the reference lists of eligible articles were hand searched.

Study selection and data extraction

Two independent investigators screened the included studies in accordance with the PRISMA guidelines for systematic reviews. Study selection was performed as outlined in the previously published protocol (14).

Only articles comparing CC and PC for the definitive management of critically ill patients with AC were included for meta-analysis.

The data extracted from the selected articles included: publication language, year and country of origin, size of study population, study design, type of intervention (PC/CC), length of hospital stay in days, morbidity and mortality rates, re-intervention, readmission for biliary complaints, and cost of treatment.

Assessment for risk of bias and statistical analysis

Two investigators independently assessed risk of bias of all the studies included. As per the instructions outlined in the Cochrane Handbook for Systematic

Reviews of Interventions, the Newcastle–Ottawa Scale was used to assess quality of non-randomized data (15). Statistical analysis was performed only on extracted data from the selected articles. The meta-analysis was done on R 64 bit version 3.2.2 using the metafor package (16). Where possible, pooled analyses were performed to compute the odds ratio (OR) using a 95% confidence interval (CI). The degree of heterogeneity between studies was calculated for each analysis.

Results

The selection of articles for meta-analysis is summarized in the *eFigure*. No controlled studies evaluating PC vs. CC have been published so far. Six retrospective studies with a total of 337 500 patients (PC 10 045, CC 327 455) were included in the meta-analysis (17–22). The characteristics of the studies included are presented in the *Table*. All studies included were published between 2000 and 2014. The sample size ranged from 42 to 306 747 patients. Wherever available, data on publication language, year and country of origin were recorded. Data on sample size, study design, inclusion criteria, and type of intervention were available for all studies. Morbidity and mortality rates were available for all studies. Cost of treatment data were available for two studies (18, 22). Simorov et al. (22) reported an estimated cost of patient care for the initial hospital stay and all further visits to the clinic within a follow-up period of 30 days. Anderson et al. (18) reported the total cost for the initial encounter adjusted for inflation to 2010 prices. The data provided by both studies were therefore not comparable (*Table*).

Primary outcomes

In-hospital and 30-day mortality

One of the included studies reported no mortality data for cholecystectomy (21). A second study did not report

FIGURE 1a

Forest Plot

of mortality after intervention (unadjusted mortality analysis presented here).
 OR, odds ratio; 95% CI, 95% confidence interval; RE model, random-effects model

FIGURE 1b

Forest Plot

of complication rates (unadjusted odds ratios presented here).
 OR, odds ratio; 95% CI, 95% confidence interval; Compl., complication rate; RE model, random-effects model

adjusted mortality odds (17). Three studies had mortality counts < 5 in one or both arms making statistical inference difficult (17, 20, 21). 30-day mortality was reported in only one study (17). Only one study was in favour of PC over CC with regard to mortality (19). Pooled results provided very strong evidence against the null hypothesis with significantly higher odds of mortality in the PC group in comparison to the CC group. Similar results were obtained on pooled unadjusted mortality analysis (OR: 4.28; 95% C [1.72; 10.62], $p = 0.0017$) (Figure 1a).

Rate of complications

All but one study reported complication rates (17). Two studies reported adjusted odds ratios for complications (18, 22). Pooled results did not identify any statistically significant difference amongst PC and CC with regard to complications (95% CI [0.36; 1.53], $p = 0.42$), Figure 1b. The pooled adjusted odds ratios for complications

(from two studies) slightly favored PC (OR 0.44; 95% CI [0.21; 0.93], $p = 0.0327$).

Secondary outcomes

Length of stay

Length of stay (LOS) was available for all studies. The mean LOS was significantly shorter in patients managed with cholecystectomy in comparison to those managed with percutaneous cholecystostomy (OR 1.41; 95% CI [1.02; 1.95], $p = 0.0401$) (Figure 2a).

Re-intervention

Re-intervention information was available for three studies (17, 20, 21). Re-intervention was defined as any surgical, endoscopic or radiological procedure aimed at addressing complications of the primary intervention (CC or PC). Only one study favoured PC with regard to re-intervention (17). Pooled results did not show any difference amongst both arms with regard to re-intervention (Figure 2b).

Forest plot of length of stay in hospital

(unadjusted odds ratios).
LOS, length of stay;
OR, odds ratio;
95% CI, 95% confidence interval;
RE model, random-effects model

FIGURE 2a

Forest plot of re-intervention following PC or CC

(unadjusted odds ratios).
OR, odds ratio;
95% CI, 95% confidence interval;
RE model, random-effects model

FIGURE 2b

Readmission

Readmission data for biliary reasons (cholecystitis, biliary colics, cholangitis, pancreatitis, or catheter slippage) was available in three studies (19–21). Pooled results provided strong evidence against the null hypothesis with higher rates of readmission in the PC group (OR 2.16; 95% CI [1.72; 2.73], $p < 0.0001$) (Figure 2c).

Discussion

This systematic review was conducted to investigate the benefit of PC in comparison to CC in the management of critically ill patients with acute cholecystitis. Six studies including 337 500 patients were included in this analysis. The risk of mortality was significantly higher in the PC group compared to the CC group. The length of hospital stay was significantly longer in the PC group. There were significantly more readmissions for biliary reasons in the PC group compared to the CC group. However, no statistically significant difference was found amongst both arms with respect to complications and re-intervention.

Laparoscopic cholecystectomy represents one of the most commonly performed surgical procedures worldwide and has been shown to be the gold standard for the management of fit patients with AC (1, 23–27). On the other hand, elderly and critically ill patients undergoing cholecystectomy for AC might be at high risk for conversion from laparoscopic to open surgery, complications (especially bile duct injury in over 40%), or even death (over 4%) (28, 29). Percutaneous cholecystostomy has been recommended as an option for the management of this subgroup of patients (8, 9, 30).

While high success rates of over 90% with a procedural mortality of just 0.5% have been reported in some small retrospective series for PC, large case-control studies have reported high rates of morbidity, mortality (up to 5%), and readmission in patients managed with PC (10, 31). In a systematic review from 2009, Winbladh et al. reported an overall mortality rate of 15.4% for PC (3). The rate of mortality for emergency cholecystectomy in this systematic review was 13.0%. The authors chose not to compare complication rates after PC with those after CC due to uncertainty with regard to the quality of reported data. Nonetheless,

FIGURE 2c

Forest plot of readmission for biliary reasons following management with PC or CC (unadjusted odds ratios).
 RA, readmission;
 OR, odds ratio;
 95% CI, 95% confidence interval;
 RE model, random-effects model

this systematic review was inconclusive on the role of PC in the management of critically ill patients with AC.

A more recent Cochrane review by Gurusamy and colleagues (32) investigated the efficacy of PC in the management of elderly and high risk patients with AC. Two studies included 156 patients managed with PC either as an alternative to CC or as a bridging procedure prior to CC were included for analysis. No significant differences were identified between both intervention groups with regard to morbidity and mortality. Thus the current literature does not provide any solid evidence on the benefit of PC over CC in this critical subset of patients.

In contrast to the two previous reviews (3, 32), the findings from this systematic review of six studies including more than 330 000 patients suggest PC to be associated with increased odds of mortality. Mortality data included all deaths, defined as in-hospital or 30-day mortality according to whichever was reported in the individual studies. The cause of death was directly related to acute cholecystitis and no distinction was made between death during and after procedure.

Patients managed with PC were hospitalized longer than those managed with CC. The length of stay was defined as the time interval between admission and discharge with regard to the index admission. Besides, the rate of readmission for biliary complaints was significantly higher in the PC group.

There was no difference in odds of complications and re-intervention amongst both arms. This was a rather interesting finding because higher rates of complications and re-intervention would be expected following the higher odds of readmission for biliary reasons. Complications such as catheter slippage, bile leak, persistent or recurrent cholecystitis would eventually necessitate re-intervention (placement of a new PC catheter or cholecystectomy). These findings suggest that PC is comparable to CC with regard to the rate of complications and re-intervention.

Although PC has been included in most guidelines as an option for the management of critically ill patients with AC, only the Tokyo guidelines provide well-

defined criteria (grade III and partly grade II AC) for its use (8, 9). However, current evidence suggests that quite a number of patients managed with PC as per Tokyo guidelines recommendation could be candidates for primary cholecystectomy (33). Besides the indication for PC, timing with respect to symptom onset and technique (transhepatic or subhepatic) of catheter insertion seem to vary widely amongst different institutions (34). It is also not clear how long the catheter should be left in place. Furthermore, data on the fate of the patient after PC is rare. These variations make it extremely difficult to compare outcomes of PC from different centers (34, 35). Thus there is need to standardize this procedure as has long been done for cholecystectomy.

Taken together, the results of this systematic review suggest that patients undergoing PC are at increased risk for death compared to those undergoing CC. Besides, PC is associated with a longer length of stay in hospital and higher rate of readmission for biliary reasons compared to CC. However, PC is as safe as CC in the management of AC and the rate of complications and re-intervention following PC is not necessarily higher than that of CC.

Although a very large number of patients was included in this meta-analysis a number of limitations must be mentioned. First, no randomized controlled trials are available on the topic of investigation, thus all the studies included were based on a retrospective design. Therefore, the presence of unknown confounders could not be excluded. Second, it is conceivable that patients managed with PC were generally sicker compared to those managed with CC. Thus patients undergoing PC would per se have been at increased risk of poor outcomes compared to those managed with CC. This constitutes a possible major bias. Third, there was a high degree of statistical and clinical heterogeneity amongst the studies included. This divergence must be blamed on the variations in the study population of the individual studies included in this meta-analysis. Many relevant confounders such as age, sex, and concomitant conditions were inconsistently

reported and therefore were not analyzed (36, 37). Fourth, it is also possible that not all eligible articles were located by the chosen search strategy. Fifth, the majority of studies were single-centered in design, and in one case, the same group reported two studies using registry data (California Office of Statewide Health Planning and Development Patient Discharge Data and Nationwide Inpatient Sample, USA) (18, 19). This might have resulted in an overlap of included patients. However, the results of the meta-analysis remained unchanged after removal of one of these studies (18). The results reported in this study therefore need to be validated in prospective studies like the ongoing CHOCOLATE TRIAL in the Netherlands (38).

Conclusion

The benefit of percutaneous cholecystostomy (PC) over cholecystectomy (CC) in the management of critically ill patients with acute cholecystitis could not be proven in this systematic review. Percutaneous cholecystostomy was associated with a significantly higher risk of mortality, longer length of stay in hospital and higher readmission rates compared to cholecystectomy. Both interventions were comparable with regard to complications and the need for re-intervention.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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Corresponding author

Dr. med. Peter C. Ambe
 Helios Universitätsklinikum Wuppertal
 Lehrstuhl für Chirurgie II
 Universität Witten-Herdecke
 Heusner Str. 40
 42283 Wuppertal, Germany
peter.ambe@helios-kliniken.de

Supplementary material

For eReferences please refer to:

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Supplementary material to:

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Flow diagram for article selection and inclusion based on the PRISMA guidelines.

PC, percutaneous cholecystostomy

eSUPPLEMENT

Systematic searches were conducted using the Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL), MEDLINE, Embase and Scopus. We used the following keywords to search for eligible studies: (acute cholecystitis OR severe cholecystitis OR cholecystitis) AND (cholecystectomy OR laparoscopic cholecystectomy OR open cholecystectomy) AND (Cholecystostomy OR percutaneous cholecystostomy OR gallbladder drain OR gallbladder tube OR transhepatic gallbladder drain OR transhepatic gallbladder tube OR cholecystostomy tube). The search results were further categorized using the predefined selection criteria listed below.

Study type and selection

Studies comparing cholecystectomy (CC) and percutaneous cholecystostomy (PC) for the definite management of critically ill patients with acute cholecystitis (AC) irrespective of the presence or absence of gallbladder stones and the use of antibiotics or supportive care were considered. Studies with PC prior to CC were not included. Since no randomized controlled trials (RCTs) exist on this topic, data for this systematic review was acquired mainly from retrospective studies. Only studies published in English language were included.

Only articles published after the comprehensive availability of modern surgical techniques (minimal invasive surgery) as well as advances in anesthesiology and intensive care medicine were included. For this reason, the search was limited to articles published after 1 January 2000. Furthermore, all series with less than 20 participants as well as case reports were excluded.

The title and abstract of each article were screened and assessed against these predetermined inclusion criteria by two independent investigators (MP and SW). The selected full-text articles were independently screened and the results were compared for concordance. All patients in the selected studies were included in the final analysis. Unclear cases were discussed with PCA. A detailed full paper assessment was performed for each study deemed eligible for inclusion. This was done independently and unblinded by MP, SAW and PCA. Disagreements were discussed with PCA and if necessary, a fourth investigator, HZ was consulted. All consensuses reached were in accordance with the protocol.

Definition of interventions

Cholecystectomy (CC) and percutaneous cholecystostomy (PC) constituted the interventions compared. Cholecystectomy (CC) was defined as the surgical removal of the gallbladder indepen-

dent of the means of access, i.e. laparoscopic or open, while percutaneous cholecystostomy (PC) was defined as the ultrasound or CT guided placement of a drain or a tube with the aim of draining the gallbladder content.

Outcomes

The primary outcomes included: in-hospital mortality, 30-day mortality and the rate of complications. Only procedure-related complications were analyzed. Secondary outcomes included: the rate of re-intervention (any form of surgical, endoscopic or radiological intervention following PC or CC), length of stay (LOS) in hospital, the rate of readmission for biliary complaints, and the cost of treatment.

Data extraction

A data extraction sheet designed for this systematic review by SK and PCA was used for data extraction. MP and SAW independently extracted data from included studies. PCA cross checked the extracted data. Disagreements were resolved in all cases via discussion. If no agreement was reached, HZ was consulted for consensus. The following information were extracted: publication language, year and country of origin, sample size, type of intervention (PC/CC), length of hospital stay (LOS) in days, morbidity and mortality rates, re-intervention rate, rate of readmission for biliary complaints, and cost of treatment.

Assessment of risk of bias

SK and MP assessed risk of bias of all the studies included. The Newcastle–Ottawa Scale was used to assess quality of non-randomized studies.

Measurement of treatment effect

Mean values and corresponding standard deviations were reported where available, and odds ratios (OR) were calculated where possible. All calculations were performed with a 95% confidence interval. The Chi-square test was employed for the calculation of significance, which was set at $p < 0.05$. Pooled estimates were presented after consideration of both clinical and methodological heterogeneity of the included studies.

Assessment of heterogeneity

The Chi-square test with a p -value of 0.05 was used to explore heterogeneity while the quantity of heterogeneity was assessed using I^2 statistics. A random effects model was used for the meta-analysis.