

Uncomplicated Acute Cholecystitis: Early or Delayed Laparoscopic Cholecystectomy?

Colecistite aguda não-complicada: colecistectomia laparoscópica precoce ou tardia?

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A B S T R A C T

Recent meta-analyses suggested that early laparoscopic cholecystectomy (within 1 week of symptom onset) for uncomplicated acute gallbladder disease is safe and feasible. However, surveys on surgical practices indicated that early laparoscopic cholecystectomy is performed by only a minority of surgeons. Furthermore, the exact time-point for performing this procedure as well as its cost-effectiveness remain a matter of debate. The TBE - CITE Journal Club performed a critical appraisal of the most relevant evidence recently published on timing of laparoscopic cholecystectomy and its cost-effectiveness for the management of uncomplicated acute cholecystitis and provides evidence-based recommendations on the topic. The literature encompasses small trials with high risk of biases. It suggests that early laparoscopic cholecystectomy is safe and shortens hospital stay. There is scarcity of well-designed and large cost-utility analyses. The following main recommendations were generated: (1) Early laparoscopic cholecystectomy should be attempted as the first-line treatment within one week of symptoms onset; and (2) The cost-effectiveness of early laparoscopic cholecystectomy should be evaluated at the individual hospital level, taking into consideration local resources such as the availability of trained personal, operating room and laparoscopic equipment.

Key words: Gallbladder. Acute disease. Cholecystitis, acute. Laparoscopy. Cholecystectomy, laparoscopic.

INTRODUCTION

Although asymptomatic in the majority of patients, gallstones may be associated with the development of significant complications, such as acute cholecystitis and biliary pancreatitis, in approximately 5% of the cases annually¹. Following the first episode of acute cholecystitis, the annual risk of gallstone-related complications can increase up to 30%²; and laparoscopic cholecistectomy (LC) is the first-line definitive surgical management. However, the exact-time point of LC for acute cholecystitis remains a matter of debate.

Early LC is usually performed within a week of the onset of symptoms, when local inflammation obscures optimal view, raising concerns about increased intra-

operative complications. Alternatively, LC can be delayed (usually for 6 weeks of symptom onset), when acute inflammation is resolved. Nevertheless, recent meta-analyses suggested that early LC (within 1 week of symptom onset) is safe and feasible^{3,4}. Furthermore, a cost-utility analysis demonstrated that early LC is less expensive and results in better quality of life when compared to delayed LC⁵. Despite the growing body of literature favoring early LC, surveys of surgical practices in the USA and UK indicated that only 30% and 20% of surgeons, respectively, perform early cholecystectomy^{6,7}.

Our TBE – CITE Journal Club performs a critical appraisal of the most relevant evidence recently published on timing of laparoscopic cholecystectomy and its cost-effectiveness for the management of uncomplicated acute

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gallbladder disease and provides evidence-based recommendations on the topic.

STUDY 1

Population-based analysis of 4113 patients with acute cholecystitis: defining the optimal time-point for laparoscopic cholecystectomy⁸.

RATIONALE

LC is the preferred surgical modality for the management of acute cholecystitis. However, controversy still exists on the best time-point when the procedure should be performed. Recent meta-analyses suggest the safety and feasibility of early (within one week of the onset of symptoms) LC. Nevertheless, a subgroup comparison of two time-points (four versus seven days after symptoms) in a meta-analysis by Gurusamy et al. was unable to demonstrate the superiority of early LC to delayed LC³. Due to the lack of studies evaluating specific time-points within the first week after onset of symptoms, the authors conducted a large population-based analysis comparing clinical outcomes after LC for acute cholecystitis at various time-points.

QUESTION

Is there a difference in clinical outcomes after laparoscopic cholecystectomy (LC) for acute cholecystitis at various time-points after hospital admission (admission day [d0]; d1; d2; d3; d4/5; de"6)? For the purpose of this article, delayed LC refers to surgery 6 or more days after hospitalization for acute cholecystitis.

MAIN FINDINGS

There is no difference in the rate of intra-operative complications between early and delayed laparoscopic cholecystectomy (OR 0.87, CI 0.39-1.94, $p=0.737$). Conversion rate to open cholecystectomy increases from 11.9% at d0 to 27.9% at de"6 for delayed LC (OR 2.86, CI 1.96-4.18, $p<0.001$). The rate of post-operative complications increase from 5.7% to 13% for delayed LC (OR 2.45, CI 1.49-4.04, $p<0.001$). The rate of reoperations increases from 0.9% to 3% (OR 3.59, CI 1.43-9.05, $p=0.007$). Post-operative length of stay also increases from 6.1 to 8 days (OR 1.31, CI 1.22-1.41, $p<0.001$). The duration of surgery was also detected to be greater (OR 1.37, CI 1.02-1.83, $p=0.036$).

STRENGTHS

- This study used prospectively collected data, which are generally more accurate than retrospectively retrieved data.
- Very large number of study subjects (4113).
- The study used a population-based database including participants from diverse settings (private clinics,

regional hospitals as well as University hospitals), which helps with the generalizability of study findings.

- The follow-up was quite impressive, with very few missing data (0.3%).
- The primary outcomes of the study are clinically relevant, as mortality is not an issue in the case of laparoscopic cholecystectomy for acute cholecystitis.
- Potential confounders such as age, gender and ASA were adjusted for.

LIMITATIONS

- The day of hospitalization was considered a surrogate for the beginning of the episode of acute cholecystitis. Although access to care is generally broadly available in a timely manner in the country where the study was undertaken, this might not be case in other health care systems universally. Therefore, the study findings may not be directly transferrable to other countries with longer times to definitive care.

- Although it is a large population-based study, the study participants are largely Caucasian, which are not the case in many other geographic regions, also limiting the extrapolation of study results to diverse ethnical groups.

- The authors do not provide demographics and baseline characteristics of patients operated on the different days to reassure balanced groups with respect to prognostic factors. In spite of adjusting for potential confounders (age, gender and ASA), unmeasured confounders (comorbidities such as diabetes or cirrhosis, the use of specific medications such as steroids etc.), cannot be totally ruled out.

- Though the use of composite endpoints, such as postoperative complications are generally useful, large number of patients (from large databases) tend to find statistically significant differences that have to be interpreted with caution considering their clinical relevance. In addition, a significant proportion of postoperative complications are classified as "other complications", making any conclusion regarding their clinical relevance extremely challenging.

STUDY 2

Prospective randomized trial using cost-utility analysis of early versus delayed laparoscopic cholecystectomy for acute gallbladder disease⁹.

RATIONALE

Although the safety of early laparoscopic cholecystectomy has been established, there have been no randomized trials assessing its cost-effectiveness. In acute gallbladder disease, due to its relatively high prevalence but overall favorable prognosis with extremely low mortality rates, coupled with shortened resources in health care

systems, cost-effectiveness may be considered as important as patient safety.

QUESTION

What is the cost-utility of early laparoscopic cholecystectomy versus conventional management of newly diagnosed biliary colic and acute cholecystitis analyzed in a setting of a prospective randomized trial?

MAIN FINDINGS

This cost – utility analysis found no significant difference in the costs or outcomes of early laparoscopic cholecystectomy versus conventional management for patients with newly diagnosed acute gallbladder disease. The mean total costs of care were £ 5911 and £6132; and societal costs were £1322 and £1461 for the early group and the conventional group, respectively. However, the incremental cost per additional quality-adjusted life year (QALY) gained (calculated 30 – 35 days after laparoscopic cholecystectomy in both groups) favoured conventional management at a cost of £3810 per QALY gained.

STRENGTHS

- Formal health economic analysis in a setting of a prospective randomized control trial, which allows a more accurate estimate of costs. A detailed data collection was performed taking into consideration costs within the inpatient environment, and outpatient visits. Indirect non-medical costs were also estimated, and included time off work, cost of travel to and from hospital, visits to primary care facilities related to gallbladder disease, and over-the-counter or prescription costs.

- The trial was registered publicly; and study outcomes and sample size clearly determined “*a priori*”, which adds to the credibility of this analysis.

- Analysis was by intention-to-treat comparison of the groups as randomized, which usually is more appropriate to reflect normal clinical practice.

- Randomization process was clearly described. Although allocation of treatment was concealed from the investigators and the patients, which is important to avoid potential biases, for obvious reasons neither of them could be blinded to the treatment itself.

- Discharges – important factor influencing hospital costs - were decided by physicians not involved with the trial.

LIMITATIONS

- Study was terminated prematurely, recruiting only 52% of its original planned sample size. The interim analysis found an unexpected small cost difference (10-fold smaller than the difference assumed for sample size calculation) between study groups. Additionally, recruitment was also unexpectedly slow. Therefore, the authors decided to terminate the trial after a total of 72 patients had been recruited. Early termination of clinical trials decreases the

power of the study in showing a given difference between study groups, and is known risk for a type II error (i.e. concluding that there is no true underlying difference when there really is one).

- Although hospital discharge was decided by independent physicians, no criteria were in place during the study, which allows for practice variation among physicians. Thus, one cannot entirely rule out practice differences between study groups.

- The follow-up period for assessment of QALY was of only 30-35 days after the cholecystectomy, which might be considered inadequate by some. Longer follow-up periods for assessment of quality of life are usually more informative.

STUDY 3

Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis³.

RATIONALE

Although previous meta-analyses of randomized controlled trials of early LC versus delayed LC during acute cholecystitis have concluded that early LC is safe and decreases the length of hospital stay, LC is mainly performed after the acute episode in many countries. This meta-analysis was conducted to include the most recent RCTs not included in previously published Cochrane review addressing timing for LC in acute cholecystitis.

QUESTION

Should patients with acute cholecystitis be offered early LC (within 7 days of onset of symptoms) or delayed LC (after an interval of at least 6 weeks following the symptom onset)?

MAIN FINDINGS

Seven RCTs were included in the systematic review, and 5 were included in the meta-analysis. Patients were randomized to early LC (223) and to delayed LC (228). No imbalance in baseline characteristics of the two groups was found.

No significant difference between the two groups (RR 0.64; 95% CI: 0.15 - 2.65; p=0.54) with respect to bile duct injury was found (injury rate was 0.5% in the early group versus 1.4% in the delayed group). There was no significant difference between the two groups regarding conversion to open cholecystectomy (RR 0.88; 95% CI: 0.62 - 1.25; p=0.47). The conversion rate was 20.6% in the early group and 23.6% in the delayed group. No significant differences were noted between groups concerning intra-abdominal collections requiring interventions, superficial wound infections, or deep wound infections. The mean total hospital stay ranged from 4.1 to 7.6 days in the early

group and from 8.0 to 11.6 days in the delayed group. In 17.5% of patients in the delayed LC group, symptoms neither did not resolve nor recurred before the planned operation; and an emergency surgery was necessary.

STRENGTHS

- Overall, the study was conducted in a methodologically-sound fashion; it utilized a very inclusive and extensive search strategy; conducted rigorous and established assessment of the risk of bias of the studies included; and assessed agreement between the two independent authors who conducted the trial selection and data extraction.

- Quasi RCTs were excluded; which are more susceptible to biases than RCTs.

- There was no heterogeneity among the trials as denoted by the χ^2 and I^2 values.

- Fixed effects statistical models and random effect statistical models were used to identify differences in the effect estimates in the entire group.

- Subgroup analysis and sensitivity analysis were performed to assess whether the effect estimates were altered in the subgroups.

- Publication bias was explored with a funnel plot. No publication bias was found.

LIMITATIONS

- Major limitations are related to the original studies included in this review.

- Risk of bias - Blinding was not performed in any of the trials, consequently they were considered to be at high risk of bias.

- Publication bias - Funnel plot did not show publication bias, but there were too few trials to perform the Egger's test for exploration of bias.

- Dataset was not sufficiently large to definitively demonstrate small differences in bile duct injury rates between an early or delayed approach to acute cholecystitis.

- High risk type I error (erroneously concluding that an intervention is beneficial when it is not) and type II

(erroneously concluding that an intervention is not beneficial when it actually is) errors because of the few trials included and the small sample in each trial.

TBE – CITE CONCLUSIONS

The conclusions are based on the most recent and relevant literature on the topic, including but not limited to a large population-based study, a cost-utility analysis in a setting of a randomized controlled trial, and a recent systematic review and meta-analysis:

1. The most relevant literature on optimal timing for laparoscopic cholecystectomy in acute gallbladder disease encompasses small trials with high risk of biases; and thus no definitive conclusion can be drawn at this point in time.

2. In uncomplicated acute gallbladder disease, current and limited evidence suggests that early laparoscopic cholecystectomy is safe and shortens hospital stay.

3. Due to the scarcity of well-designed and large cost-utility analyses, the cost-effectiveness of early laparoscopic cholecystectomy remains unclear. The cost-effectiveness of early LC should be evaluated in a setting-specific fashion; considering the availability of 24hr-operating room, trained medical staff and laparoscopic equipment.

TBE – CITE RECOMMENDATIONS

1. Early laparoscopic cholecystectomy should be attempted as the first-line treatment within one week of symptoms onset for uncomplicated acute gallbladder disease.

2. The cost-effectiveness of early laparoscopic cholecystectomy should be evaluated at the individual hospital level, taking into local resources such as the availability of trained personal, operating room and laparoscopic equipment.

3. Further research should be focus on the defining appropriate time-points since the onset of symptoms and its cost-effectiveness in different health care systems/ countries.

R E S U M O

Metanálises recentes sugerem que a colecistectomia laparoscópica precoce (dentro de uma semana do início dos sintomas) para a doença aguda, não complicada, da vesícula biliar é segura e viável. No entanto, enquetes sobre as práticas cirúrgicas indicam que a colecistectomia laparoscópica precoce é realizada por apenas uma minoria dos cirurgiões. Além disso, o melhor momento para realização deste procedimento, bem como sua relação custo-eficácia continuam sendo uma questão de debate. A reunião de revista TBE - CITE realizou uma avaliação crítica dos artigos mais relevantes, publicados recentemente, sobre o momento da colecistectomia laparoscópica e sua relação custo-eficácia para o tratamento da colecistite aguda não complicada e fornece recomendações baseadas em evidências sobre o tema. A literatura engloba pequenos ensaios com alto risco para vieses. Ela sugere que colecistectomia laparoscópica precoce é segura e encurta o período de internação. Há uma escassez de estudos bem desenhados e de grandes séries analisando custo-utilidade. As seguintes recomendações foram geradas: (1) a colecistectomia laparoscópica precoce deve ser tentada como o tratamento de primeira linha dentro de uma semana do início dos sintomas, e (2) O custo-efetividade da colecistectomia laparoscópica precoce deve ser avaliada em cada local, levando-se em consideração os recursos, tais como a disponibilidade de pessoal treinado e de equipamentos laparoscópicos.

Descritores: Vesícula biliar. Doença aguda. Colecistite aguda. Laparoscopia. Colecistectomia laparoscópica.

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STATEMENT

The opinions and assertions contained herein represent the private views of the participants of the Evidence-based Telemedicine - Trauma and Acute Care Surgery (TBE - CITE) Journal Club, and are not to be construed as reflecting the views of the institutions that they represent.

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