Title

Recurrence of the acute cholecystitis after of EUS-guided gallbladder drainage versus cholecystectomy in elderly patients: A multicentre randomized controlled trial)

CHOICE trial

(**CH**olecystitis **O**utcomes in the **I**nvestigation of **C**holecystectomy versus **E**US-GBD)

Names of contributors:

Lauri Pautola, MD

Ville Liukkonen, MD

Heikki Karjula, MD PhD

Tellervo Ylimartimo, MD PhD

Antti Kivivuori, MD PhD

Hannes Kortekangas, MD

Heikki Huhta, MD PhD

Abstract

Background: Acute cholecystitis is common in the elderly, with increasing incidence with age. The gold standard treatment is laparoscopic cholecystectomy (LCC), yet antibiotics alone fail in ~20% of cases, with high recurrence rates (50% in two years). Endoscopic ultrasonography-guided gallbladder drainage (EUS-GBD), using lumen-apposing metal stents (LAMS), offers a promising alternative, with fewer complications and reinterventions than PT-GBD in studies. However, direct comparisons between LCC and EUS-GBD are scarce, with only one study reporting no significant differences. This protocol aims to address this gap.

Methods: The study is a multicenter, randomized controlled trial comparing EUS-GBD to LCC for acute cholecystitis in patients aged ≥75 years. The primary endpoint is the 2-year recurrence rate of cholecystitis, with a sample size of 116 patients (including 10% dropout). Patients are randomized 1:1 using computer-generated blocks, and outcomes are analyzed primarily by a intention-to-treat approach. EUS-GBD is performed with LAMS, while LCC follows standard operative protocols. Secondary endpoints include complications (Clavien-Dindo), length of stay, ICU days, reoperations, readmissions, and mortality. Data collection is through REDCap, and subgroup analyses include factors like age >85, CCI ≥4, and ASA ≥4. Interim analysis will terminate the trial if major complications exceed thresholds. Statistical methods include χ^2-tests, t-tests, Kaplan-Meier survival, and logistic regression. Results are managed in a secure database, ensuring confidentiality, with ethical approval from Oulu University Hospital.

Discussion: This trial evaluates whether EUS-GBD, a minimally invasive alternative, is non-inferior to LCC for acute cholecystitis in elderly patients. While LCC is the gold standard, EUS-GBD may offer benefits like avoiding general anesthesia and reducing hospital stays. The trial's robust design, including recurrence rates and complications as endpoints, ensures reliable comparisons. If EUS-GBD proves similarly effective, it could provide a valuable option for eldery. This trial has the potential to significantly impact clinical practice, offering improved management strategies for elderly patients with acute cholecystitis.

Background

Acute cholecystitis is a common condition in the elderly, with its incidence increasing exponentially with age (1). The widely accepted gold standard treatment is early, preferably laparoscopic, cholecystectomy (LCC) (2). However, acute cholecystitis can sometimes be managed with antibiotics alone, although the treatment failure rate is approximately 20-30% (2). As a result, planned operations are typically not urgent in most cases.

In high volume hospitals, the waiting time from admission to the operating room (OR) is typically 3–5 days. During this waiting period, patients receive antibiotics and are usually fasting as they await surgery. For elderly patients, this prolonged fasting period can be particularly challenging.

Nevertheless, since up to 50% of patients require an intervention in addition to antibiotics, the risk of cholecystitis recurrence remains significant. Approximately 50% of patients experience a recurrence within two years, and 20–30% may suffer three or more episodes within that timeframe if treated with antibiotics alone (2). Consequently, surgery appears justified, as it can significantly reduce long-term morbidity and mortality.

Endoscopic ultrasonography-guided gallbladder drainage (EUS-GBD) has recently gained attention as an alternative to PT-GBD. This procedure typically employs an electrocautery-enhanced LAMS (3). Currently, three devices are available for this technique: Hot-Axios (Boston Scientific, Marlborough, Massachusetts, United States), Hot-Spaxus (Niti-S, Taewoong Medical, South Korea), and Hot-Plumber (Hanarostent, M.I.Tech, South Korea). These instruments allow for a one-step procedure, reducing the risk of content spillage from a non-adherent gallbladder compared to the multistep approach involving tract dilation.

Numerous comparative studies have demonstrated the efficacy of EUS-GBD in both the short- and mid-term (4). A recent randomized controlled trial (5) reported that EUS-GBD was associated with fewer adverse events (26% vs. 78%), 30-day reinterventions (2.6% vs. 30%), readmissions (15% vs. 50%), and cases of recurrent cholecystitis (2.6% vs. 20%) at one-year follow-up compared with PT-GBD. Similar findings were reported in a meta-analysis comparing EUS-GBD and PT-GBD (6).

The landmark CHOCOLATE trial (7), involving 142 patients, compared LCC with PT-GBD. Patients

who underwent LCC demonstrated similar mortality rates (3% vs. 9%) but experienced fewer major complications (12% vs. 65%), less recurrent biliary disease (5% vs. 53%), and shorter hospital stays (5 vs. 9 days).

However, direct comparisons of LCC and EUS-GBD remain limited. To date, only one previous study involving 60 patients has compared these two approaches, reporting no significant difference in outcomes, with the complication rate being identical (8). Moreover, our yet unpublished data from a propensity-matched retrospective study comparing LCC and EUS-GBD, each group comprising 100 patients—the largest series in this area to date—indicates a higher rate of major complications in the LCC group (19% vs. 9%). Furthermore, the median procedure time for EUS-GBD was only 16 minutes, compared to 103 minutes for LCC. This does not include the time required for patient and anesthesia preparation, induction of anesthesia, and recovery from anesthesia.

Objectives

Since emergency LCC availability is limited in the Finnish healthcare system, and EUS-GBD can be performed with reduced waiting times, it might further shorten hospital stays and cumulative operation times, leading to societal savings in both direct and indirect costs. The primary objective of this study is to determine whether EUS-GBD is non-inferior to cholecystectomy with respect to the recurrence rate of cholecystitis among elderly patients.

Trial design:

The study is a multicenter, randomized controlled trial conducted in the four hospitals of Finland.

Eligibility criteria

Inclusion Criteria

- Patients aged 75 years or older with radiologically confirmed acute cholecystitis and elevated inflammatory parameters.
- Patients able to provide informed written consent.
- Patients capable of completing questionnaires during follow-up.

Exclusion Criteria

- Age under 75 years.
- Patients unfit for surgery.
- ASA score below 3.
- Unwillingness to participate in follow-up assessments.
- Lack of informed consent.
- Clinical frailty scale of 8 or over

Who will take informed consent?

Investigator or research nurse at the surgical ward during index admission.

Additional consent provisions for collection and use of participant data and biological specimens

Data collected within the CHOICE trial is used only for the purposes determined in the protocol. All modifications to protocol will be communicated with Oulu University Hospital Ethics committee by amendments.

Interventions

Explanation for the choice of comparators

Currently, LCC is considered the gold standard for the treatment of acute cholecystitis. However, results from EUS-GBD have been highly promising. Unlike LCC, EUS-GBD does not require general anesthesia or an operating room (OR), significantly enhancing its accessibility. The direct cost of LCC is estimated at €3,436, while the cost of EUS-GBD is €4,500. When considering additional expenses associated with LCC, such as prolonged surgical ward stays (e.g., €1,821 for three days), cumulative OR time, and extra on-call fees, the potential advantages of EUS-GBD justify further investigation.
The primary aim of this study is to evaluate whether EUS-GBD is an equally effective treatment modality for elderly patients. A key consideration in designing the intervention is its seamless integration into current clinical practice if proven beneficial. According to the existing study protocol, no additional hospital visits are required, and follow-up is conducted through phone calls

by a research nurse.

Intervention description

In both group intra venous antibiotics will be started at the point of patients' admission to hospital. Post-procedural antibiotics are continued depending on the severity of acute cholecystitis, based on the clinician's assessment.

Laparoscopic cholecystectomy for acute cholecystitis is performed according to each hospital's standard operative protocol. Briefly, a four-port laparoscopic technique is utilized. The gallbladder is lifted from the fundus, and the cystic duct and cystic artery are dissected as separate structures. The posterior wall of the gallbladder is detached from the gallbladder bed in the liver, ensuring the critical view of safety is achieved. Once this step is completed, the cystic duct and artery are clipped and divided. The gallbladder is then removed from the gallbladder bed, and the specimen is extracted through one of the port incisions.

EUS-GBD is performed under propofol-induced anesthesia, without airway secure or deeper sedation. The EUS scope is advanced through the esophagus into the stomach and duodenum after the patient is anesthetized. The gallbladder is identified using ultrasound, and the optimal position for LAMS insertion is determined. The primary approach is via the transduodenal route (cholecystoduodenostomy). If a safe cystotome puncture cannot be achieved through this route, the transgastric approach (cholecystogastrostomy) is used. The operator selects the appropriate LAMS based on the clinical situation, with a 15 mm wide LAMS being the standard choice in most cases.

The possibility of common bile duct (CDB) stones is evaluated during procedure. Applicable methods during surgery are intraoperative cholangiography and laparoscopic ultrasonography. Evaluation during EUS-procedure is by ultrasonography. If CBD-stones are found during surgery, they are removed either laparoscopically - when feasible - or by intra/postoperative ERCP. CBD-stones found during EUS-examination are removed during the same session with ERCP.

As a general rule, the LAMS is replaced with a plastic pigtail stent six months after the procedure, once the gallbladder has fully adhered to the duodenal or gastric wall and a mature fistula has formed. This replacement is performed during a separate outpatient clinic visit and is intended to be a permanent solution. However, if the patient's life expectancy is estimated to be less than two years, as assessed by the operator, the LAMS can be left in place as a permanent solution without further stent placement.

Criteria for discontinuing or modifying allocated interventions

Not applicable.

Strategies to improve adherence to interventions

Enhancing adherence requires clear communication, patient engagement, and simplified processes. Tailoring education, leveraging technology like reminders, and integrating follow-ups ensure accessibility.

Relevant concomitant care permitted or prohibited during the trial

Participants can continue their routine care during the trial (e.g., treatment for chronic conditions) as it does not interfere with the study's objectives or outcomes. Except for anticoagulation medications, which are paused in both groups before the intervention. Generally, DOACs and Warvarin are paused 2 days prior, and antiplatelet medications 5 days prior. However, for well-justified reasons, the pause durations may vary, with the final decision made by the interventionist.

Provisions for post-trial care

Not applicable.

Outcomes

<u>Primary Outcomes:</u>

This trial evaluates two primary outcomes. The first primary outcome is the 2-year recurrence rate of cholecystitis after the intervention, diagnosed based on radiological findings and elevated

inflammatory parameters. The second primary outcome is the length of hospital stay, measured from the patient's admission to discharge.

Secondary outcomes:

The secondary outcomes are listed below. The mean/median depending on the normality of the outcome will be compared between the groups.

- length of antibiotic treatment
- length of ICU stay
- postoperative complications according to Clavien Dindo-classification
- organ specific postoperative complications
- bile surgery and EUS specific complications
- 90-day mortality
- long term mortality
- long term recurrence
- direct hospital costs

Possible confounders

Patients' general condition might be a potential confounder, as precise classification is challenging based on rough parameters such as ASA, Charlson Comorbidity Index, age, and sex. However, since the sample size is feasible, the random effect should occur, meaning these factors will be accounted for through the randomization process.

Participant timeline

The following data will be recorded prospectively by using specific electronic case report forms.

Baseline

- Age (at the time of operation)
- Sex: male – female
- Charlson Comorbidity Index: 0, 1, 3 ≥4 (Table 1)

- NRS2002
- BMI
- ASA
- Clinical frailty scale
- WHO
- smoking status/ amount
- Anticoagulation therapy
- self-reported walking distance
- Preoperative laboratory values (Hb, leukocytes, creatinine, CRP, liver enzymes, INR)
- Severity of acute cholecystitis (grade I, II and III)
- Antibiotics started during hospital admission
- Time from presentation to procedure, hours

Intervention data

- Duration of procedure
- Conversion percentage of LCC
- Complicated cholecystitis (perforated, peritonitis, abcess, emphysematous or ischaemic or gangrenous cholecystitis, CBD stones, hemobilia)
- Intraoperative bleeding
- Intraoperative transfusions
- Additional procedures during same session
- Technical success
- Clinical success
- Intraoperative complication

Primary hospital stay and discharge

- All complications during the hospital stay measured by
    - Clavien-Dindo classification
    - Organ specific
    - Bile surgery specific
    - EUS specific

- Re-operations or interventions related to the primary procedure or cholecystitis recurrence within 1, 2, and 5 years.Length of stay (LoS)
- Discharge to home or another healthcare unit
- ICU days
- 30- and 90-day readmission rates
- 1-, 2-, 5-, and 10-year acute cholecystitis rates
- 30d and 90d mortality
- Long term mortality

Sample size

According to the only published study on this topic (8), a propensity-matched retrospective study by Teoh et al., the recurrence rate of cholecystitis is 0% after LCC and 3.3% after EUS-GBD, a difference that is clinically acceptable. The first primary endpoint is the recurrence rate of cholecystitis within 2 years, assessed in the intention-to-treat population. If there is a true difference in favour of the experimental treatment of 3.3% (3.3% vs 0%), then total of 104 patients are required to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the standard group of more than 4%.

The second primary endpoint is the length of stay. Assuming a mean difference of 2 days with a standard deviation of 3, favoring the EUS-GBD arm, a total of 94 patients are required to achieve 90% power with an alpha level of 0.05.

To account for a 10% dropout rate, a total of 116 patients will be recruited.

All analyses will be performed by or under the guidance of a professional statistician and following the CONSORT guidelines.

Recruitment

All eligible patients will be offered enrolment in the study at the surgical ward after hospital admission due to acute cholecystitis. A screening log of all acute cholecystitis treated in participating

hospitals is maintained for further assessment of selection biases. After receiving the proper information on the possible advantages and disadvantages of the intervention, and signing the informed consent, the subject will be enrolled. Participating investigators are qualified EUS-performing surgeons experienced in conducting EUS-GBD. LCC is performed by the on-call gastrointestinal surgeon or surgical resident working at the participating hospitals.

Concealment mechanism

Data is collected directly into a digitalized database, REDCap, which is a secure web application for building and managing online databases. It is specifically geared to support online and offline data capture for research studies and operations. Oulu University Hospital ethical committee has approved the level of REDCap data protection.

Implementation

Patients are randomly assigned in a 1:1 ratio to either the intervention group or the control group using REDCap's automated, computer-generated randomization module. The module implements a pre-defined allocation table (CSV) uploaded to REDCap prepared by a study principal investigator. It supports stratified, permuted-block randomization (e.g., by center), with role-based permissions controlling who can trigger randomization. All participating centers use a single REDCap project and perform randomization before adding new cases, ensuring centralized randomization and balanced allocation across arms

Data collection and management

Plans for assessment and collection of outcomes

All collected variables are defined in detail in the database. Numbers of missing data will be reported for each variable. The data collection will be the responsibility of the principal investigator and will be reviewed by the study group.

Data management

A electronic database is prospectively maintained throughout the study period. Secure access to the database is granted only to participating investigators. All eCRFs are handled with a special trial ID and date of birth. Data collected during the study will be stored for 10 years after the publication.

Log in history, saved data, and double data entries can be tracked, if necessary. Data ranges are predetermined.

Confidentiality

Patient confidentiality will be strictly maintained. Patients will be assigned a study ID, and all data will be managed without names or personal social security numbers. Access to patient records is limited to the study group and the investigator-delegated study coordinator.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

Not applicable.

Statistical methods for primary and secondary outcomes

All analyses will be performed primarily according to the intention-to-treat (ITT) principle, in which all randomized patients are included in the analyses. Due to the recruitment method, some patients who should not have been recruited might be also randomized. The most common reasons might include patients who are not adequate candidates for LCC or cases where EUS-GBD was not performed due to an intraprocedural decision. A modified ITT (mITT) analysis will be performed excluding these patients. In accordance with the study protocol, an analysis based on the treatment received, referred to as the As-Treated (AT) analysis, will also be conducted.

The primary endpoint will be the recurrence rate (%) of acute cholecystitis within 2 years between the study groups. Secondary outcomes have been listed previously. The primary endpoint, as well as other categorical data, will be analyzed using the χ^2-test or Fisher's exact test. Student's t-test or Welch's test will be used for continuous variables, with the latter applied if the assumption of homogenous variances does not hold. Logistic regression will provide odds ratios (ORs) with 95% confidence intervals (CI), and survival outcomes will be analyzed using Cox regression to provide hazard ratios (HRs) with 95% CI. Overall survival rates will be compared using Kaplan-Meier analysis and the log-rank test.

Multiple imputations for missing outcome data will be employed for sensitivity analyses. Prospectively planned subgroup analyses are listed below. Sample size calculation was performed only for the primary endpoint, and subgroup analyses are hypothesis-generating only. Statistical analysis will be conducted using R-statistical software v.4.3.1.

Interim analyses

Since EUS-GBD is a newly evaluated treatment modality compared to the gold standard for elderly patients with acute cholecystitis, an interim analysis will be performed after the first 40 patients in each group. The major complication rate and the rate of cholecystitis recurrence will be assessed. If the major complication rate is 10% higher in the experimental group or if the acute cholecystitis rate exceeds 20%, the trial will be terminated.

Methods for additional analyses (e.g. subgroup analyses)

The prospectively planned subgroup analyses are as follows: age over 85 years, CCI ≥ 4, ASA ≥ 4, LCC performed by a specialist, and excluding patients who died within 180 days post-procedure. However, the sample size calculation will only be performed for the primary endpoint, and subgroup analyses are hypothesis-generating only.

Composition of the coordinating center and trial steering committee

The trial steering committee is composed of the Chief of Surgery, Adjunct Professors of Gastrointestinal Surgery, four consultants, a biostatistician, and a research nurse. The first author and the research nurse are responsible for the day-to-day management of the trial. As the trial is free of industrial sponsorship and no professional steering committees exist in Finnish hospitals, no commercial steering committee has been appointed.

Composition of the data monitoring committee, its role and reporting structure

As the trial is independent from industrial sponsorship, and due to lack of professional data monitoring committees in Finnish hospitals, no data monitoring committee is required. The collected data is monitored by the first author, and research nurse to ensure completeness.

Dissemination plans

The protocol of the trial will be registered and published at the beginning of the trial. The results are planned to be published as the recruitment and 30-day follow-up are completed.

Bibliography

Kärkkäinen JM, Lehtimäki TT, Manninen H, Paajanen H. Acute Mesenteric Ischemia Is a More Common Cause than Expected of Acute Abdomen in the Elderly. J Gastrointest Surg. 2015 Aug;19(8):1407–14.
2. Okamoto K, Suzuki K, Takada T, Strasberg SM, Asbun HJ, Endo I, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepato-Biliary-Pancreat Sci. 2018 Jan;25(1):55–72.
3. Teoh AY, Perez-Miranda M, Kunda R, Lee SS, Irani S, Yeaton P, et al. Outcomes of an international multicenter registry on EUS-guided gallbladder drainage in patients at high risk for cholecystectomy. Endosc Int Open. 2019 Aug;07(08):E964–73.
4. Teoh AB. Outcomes and limitations in EUS-guided gallbladder drainage. Endosc Ultrasound. 2019;8(7):40.
5. Teoh AYB, Kitano M, Itoi T, Pérez-Miranda M, Ogura T, Chan SM, et al. Endosonography-guided gallbladder drainage versus percutaneous cholecystostomy in very high-risk surgical patients with acute cholecystitis: an international randomised multicentre controlled superiority trial (DRAC 1). Gut. 2020 Jun;69(6):1085–91.
6. Luk SWY, Irani S, Krishnamoorthi R, Wong Lau JY, Wai Ng EK, Teoh AYB. Endoscopic ultrasound-guided gallbladder drainage versus percutaneous cholecystostomy for high risk surgical patients with acute cholecystitis: a systematic review and meta-analysis. Endoscopy. 2019 Aug;51(08):722–32.
7. Loozen CS, van Santvoort HC, van Duijvendijk P, Besselink MG, Gouma DJ, Nieuwenhuijzen GA, et al. Laparoscopic cholecystectomy versus percutaneous catheter drainage for acute cholecystitis in high risk patients (CHOCOLATE): multicentre randomised clinical trial. BMJ. 2018 Oct 8;k3965.
8. Teoh AYB, Leung CH, Tam PTH, Au Yeung KKY, Mok RCY, Chan DL, et al. EUS-guided gallbladder drainage versus laparoscopic cholecystectomy for acute cholecystitis: a propensity score analysis with 1-year follow-up data. Gastrointest Endosc. 2021 Mar;93(3):577–83.