

Official title: Randomized multicentre double-blind clinical trial comparing ERCP vs ERCP and transmural vesicular drainage in non-surgical patients with symptomatic choledocholithiasis

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## Abstract

Cholelithiasis occurs in 10-20% of the general population. Up to 18% of these subjects will present symptoms. In patients with symptomatic choledocholithiasis who are not candidates for surgery with indication for ERCP, transmural drainage of the gallbladder reduces the risk of recurrence.

We propose a multicentric double-blind randomized trial. Our primary objective is to assess whether ERCP associated with transmural gallbladder drainage is able to reduce biliary disease income compared with ERCP in patients not candidates for surgery with symptomatic choledocholithiasis and cholelithiasis during one year of follow-up. Also we will analyze the proportion of technical success and complications.

The study population includes all patients older than 75 years with symptomatic choledocholithiasis. An estimated 75 subjects per group (ERCP alone and ERCP and transmural drainage) are needed.

## 1. Introduction

### Importance of the pathology associated with biliary lithiasis

Cholelithiasis occurs in 10-20% of the general population (1). Up to 18% of these subjects will present symptoms and, of these, 1.5% will present an episode of pancreatitis, cholecystitis or acute cholangitis (2). In this way, the pathology associated with biliary lithiasis is the first digestive cause of hospital admission (3). Fortunately, the overall mortality secondary to the pathology associated with biliary lithiasis is less than 3% (3), so their biggest problem lies in the frequency of their recurrences. It is estimated that more than 35% of the subjects who have presented a first episode of pancreatitis, cholangitis or acute cholecystitis will require a new hospital admission in the following two years in case of no intervention to reduce the risk of recurrence (4). Most of these recurrences occur in the first year since the index episode. Importantly, no association has been observed between the nature of the first episode and recurrence

### Recommended management

The treatment of the pathology associated with biliary lithiasis therefore deals with two problems, controlling the acute process and preventing new episodes. In general, laparoscopic cholecystectomy is the recommended method to reduce the risk of recurrence. In the case of mild and moderate acute cholecystitis, urgent cholecystectomy is recommended because it solves both problems in a single act (5), while in severe cases and in some moderate cases, antibiotic treatment is recommended and the vesicular content can be drained. percutaneous or endoscopic route for the acute episode and perform cholecystectomy in a deferred manner (5). In mild acute pancreatitis, cholecystectomy is also recommended during the acute

episode, while moderate and severe cholecystectomy is delayed (6). In the case of acute cholangitis, the resolution of the acute problem requires the drainage of the bile duct through endoscopic retrograde cholangiopancreatography (ERCP) (7). Therefore, in acute cholangitis and in other cases of symptomatic choledocholithiasis such as biliary colic or episodes of obstructive lithiasic jaundice, it is very common to perform two invasive procedures, ERCP to resolve the acute problem and delayed cholecystectomy to prevent recurrences.

#### Conditioning factors associated with old age

The importance of management in the elderly is primarily that they are the most affected age group. The prevalence of cholelithiasis presents a positive association with age, going from 3% in children under 30 years to 25% in women over 65 years (8). Second, they are subjects with a higher surgical risk, presenting complications associated with surgery in more than 20% of cases (9, 10). Third, depending on age and comorbidity, life expectancy can often be less than 5 years. Fourth, in patients with cognitive impairment, the decision to perform elective surgery to prevent future complications is complex. Finally, the mortality of the complications associated with biliary lithiasis increases significantly, reaching 6% in cholecystitis (10) and up to 10% in acute cholangitis (9).

#### Management in the elderly

In this way, the decrease in life expectancy and the increase in surgical risks mean that cholecystectomy is frequently dismissed, despite a high risk of recurrence with a not insignificant mortality. In our country, the proportion of patients older than 65 years with a first episode of pancreatitis, cholangitis or acute cholecystitis who does not undergo a cholecystectomy can exceed 50% of cases (9, 10). In other countries around us, the proportion of elderly people who have cholecystectomy after a first episode is also high, between 25 and 50% (4, 11, 12).

#### Alternatives to surgical treatment

All of the above has generated a demand for safer and less invasive interventions to reduce the risk of recurrence of complications of cholelithiasis (13). The mere performance of ERCP reduces the risk of new biliary complications, although much less than performing a cholecystectomy (9). Within the advanced endoscopic techniques developed in recent years, transluminal endoscopic surgery has been proposed through natural orifices (NOTES), transpapillary drainage of the gallbladder and transluminal vesicular drainage using anastomosis-forming stents (also called lumen apposing metal stents LAMS). Although cholecystectomy by NOTES has shown similar results to laparoscopic surgery in terms of complications (14), the great technical difficulty involved makes it impossible to generalize out of highly specialized centers.

The transpapillary drainage of the gallbladder consists in having a pigtail-type plastic prosthesis from the duodenum to the gallbladder, through the common bile duct and the cystic. It is a less complex technique, being feasible in approximately 80% of patients (15). The greatest limitation to achieve technical success is to move the guide through the cystic for anatomical reasons, by the inflammation itself or stone impaction. As it is not necessary to pass through hollow viscera, it may be especially useful in patients with a high risk of hemorrhage (16). The transmural drainage generally uses LAMS, which have a diabolo shape, so that they bring the two communicating hollow viscera closer together. Recent models incorporate a cutting device in the LAMS introducer catheter, allowing drainage in a single step. Several publications of our group have shown that this technique has been used successfully in patients not candidates for surgery (17-19). The technical success of transmural drainage is close to 90% (18, 19).

#### Outcome of endoscopic alternatives on the risk of recurrence

We hardly have any work evaluating the effect of available endoscopic techniques on the risk of recurrence. Walter et al published a multicenter series of 30 patients with acute cholecystitis who underwent transmural drainage, with a mean follow-up of 298 days. 7% presented a new episode of cholecystitis during follow-up (19). In another unicentric Korean series of 63 patients with cholecystitis and transmural drainage with a follow-up of 275 days, recurrences were observed in 3.6% (20). It is important to note that in both

Studies were only included as recurrences new episodes of cholecystitis. Transpapillary drainage presents a higher number of recurrences. Lee and colleagues published a series of 29 patients (21) with acute cholecystitis in whom cholecystectomy and percutaneous drainage were rejected. Technical success was achieved in 79% of patients. They identified complications during follow-up in 20%, although it must be stressed that they defined recurrence as the appearance of any biliary event.

## 2. Hypothesis

### Conceptual hypothesis:

In patients with symptomatic choledocholithiasis who are not candidates for surgery with indication for ERCP, transmural drainage of the gallbladder reduces the risk of recurrence.

### Operational hypothesis:

In subjects > 75 years with symptomatic choledocholithiasis, performing an ERCP with sphincterotomy and transmural drainage of the gallbladder vs. ERCP with sphincterotomy reduces the risk of admission due to complications of cholelithiasis during a 1-year follow-up period.

### 3. Objectives.

#### Primary objective:

- To assess whether ERCP associated with transmural gallbladder drainage is able to reduce biliary disease income compared with ERCP in patients not candidates for surgery with symptomatic choledocholithiasis and cholelithiasis during one year of follow-up.

#### Secondary objectives:

- Describe the proportion of technical successes and complications associated with transmural biliary drainage, ERCP and those associated with admission.
- Compare the proportion of income from non-biliary causes in both groups.
- Compare mortality during admission and during follow-up in both groups.
- To compare the incidence of biliary and non-biliary admissions during the follow-up year in both groups.
- Compare the hospital costs of the index income and those generated in the 12 months of follow-up between the patients assigned to the control group and the experimental group.

### 4. Design

Multicentric double-blind randomized trial

### 5. Methods

#### Study population

The study population includes all patients older than 75 years with symptomatic choledocholithiasis. This includes the pictures of acute cholangitis, obstructive jaundice or biliary colic secondary to choledocholithiasis. Participation in the study will be offered to all consecutive patients who meet inclusion criteria and do not present exclusion criteria diagnosed in the participating centers once the project is started until the estimated sample size is completed (see below). Given that in these patients the usual clinical practice is the realization of an ERCP, they will be identified from the ERCP requests received in the endoscopy units.

#### Inclusion and exclusion criteria

The inclusion criteria are:

- Symptomatic choledocholithiasis (choledocholithiasis demonstrated radiologically or highly suspected by clinical data (acute cholangitis or obstructive jaundice), analytical and imaging according to the criteria of high probability of choledocholithiasis established in the clinical guidelines (ASGE Guide).

- Age > 75.

- Discarded for surgical treatment due to age, comorbidity or refusal of the patient.

The exclusion criteria are:

- Charlson comorbidity scale adjusted to age <4.

- Prior ERCP.

- Previous episodes of cholangitis, pancreatitis or lithiasic cholecystitis.

- Hepatobiliary surgery or previous superior digestive tract.

- Ascitis.

- Inability to tolerate sedation of endoscopy, perforation of the digestive tract or other contraindication to endoscopy.

- Coagulopathy with INR > 1.5 not correctable or thrombocytopenia <50000 / mm<sup>3</sup> not correctable.

- Other diagnoses at admission (acute cholecystitis, acute pancreatitis, biliopancreatic neoplasia).

- Hemodynamic instability.

- Urgent procedure performed after hours

- No availability of expert material / endoscopist in drainage.

- Anatomical impossibility of performing biliary drainage (absence of vesicular distension, contact between gallbladder and stomach or duodenum, contact area <10 mm).

- Baseline ECOG >= 4

- Expectancy of survival <6 months.

- Refusal to participate.

- Distance between the gallbladder and upper digestive tract > 1cm, scleroatrophic vesicle, lack of stable acoustic window for drainage

Definitions used to define the primary and secondary objectives:

1. Recurrence (main endpoint): Hospital admission of biliary cause. It includes both diseases secondary to cholelithiasis (cholangitis, cholecystitis, pancreatitis, hepatic

abscess, obstructive jaundice, biliary colic) and biliary pathology secondary to endoscopic management (bile leak).

2. Technical success: endoscopic confirmation of the normoposition of the PAL by means of identification of the exit of bile through it.

3. Incidence of biliary cause: One in which between the diagnostics at discharge appears one of the items specified in the definition of recurrence.

4. Incidence of non-biliary cause: One in which between the main and secondary diagnoses at discharge none of the items specified in the definition of recurrence appear.

## Intervention

Patients who meet the inclusion criteria and do not present any exclusion criteria will be invited to participate in the study. Between the formalization of the request and the endoscopic exploration the informed consent will be completed (see annex II) according to the law 41/2002 of autonomy of the patient without that for that reason the relationship with his doctor is altered or there is any prejudice in his treatment.

### 1) Endoscopic act

It will be held at the Rio Hortega University Hospital, the University General Hospital of Alicante or the Ramón y Cajal University Hospital. First, ERCP will be performed.

Subsequently, an endoscopic ultrasound will be performed to rule out local causes of exclusion. If there is no contraindication, randomization and placement of transmural vesicular drainage will be carried out if assigned to the intervention group:

-Control group: An ERCP with biliary sphincterotomy will be performed. The performance of other techniques (balloon extraction, dilation, placement of biliary prosthesis ...) is at the expense of the endoscopist. The procedure will be performed under direct sedation with propofol controlled by the endoscopist team, and with CO<sub>2</sub> insufflation.

-Intervention group: ERCP with biliary sphincterotomy will be performed. The performance of other techniques (balloon extraction, dilation, placement of biliary prosthesis ...) is at the expense of the endoscopist. After this, transmural drainage of the gallbladder will be performed by placing a LAMS Axios (Boston Scientific) usually 15x10 mm or 10x10 mm to allow direct cholecystoscopy with a conventional gastroscope or transnasal gastroscope. The placement of the drainage will be performed in the same endoscopic act, by means of an Olympus® sectorial echoendoscope, assisted with X-rays, which allows puncturing the vesicle from the gastric antrum or the duodenal bulb to generate a cholecysto-gastrostomy or cholecysto-duodenostomy respectively. After the puncture of the vesicle from the most optimal anatomical point,

it will be tutored with guidance and a Hot Axios® LAMS will be placed on it to generate the anastomosis between the aforementioned structures. After the placement of the prosthesis, it will be subject to the decision of the endoscopist to perform cholecystoscopy to perform the maneuvers it deems appropriate (extraction of stones, taking biopsies, resection of polyps ...). The performance of both procedures will be performed under direct sedation with propofol controlled by the endoscopist team, and with CO2 insufflation, according to the usual practice of the HURH Endoscopy Unit.

## 2) Hospitalization:

After the procedure, the hospital management is in the hands of its responsible physicians in plant at the requesting center. A report will be delivered that does not show if the patient has had the LAMS implanted or not. Therefore, physicians responsible for plant management will not receive information about the assigned group or whether transmural vesicular drainage has been performed.

## C.3) Follow-up:

It will be held in each of the participating centers. It will consist of 4 face-to-face visits (after 1 day, 3 months, 6 months and 12 months after the procedure) and 2 phone calls (7 days after the procedure and 9 months). In the case of institutionalized patients or those with serious mobility problems, in-person visits may be made by telephone in an exceptional manner. The physician responsible for the follow-up will be blinded as to the procedure performed (it will not be specified if transmural drainage was performed in the endoscopic report, nor will images of the drainage be included in the discharge report available in the electronic medical record until after the completion of the study or if complications are suspected). During the follow-up visits, it will be confirmed that the prosthesis remains normalized by abdominal ultrasound. The physician responsible for the follow-up will only be notified of the arm to which the patient has been assigned (and of the results of the tests to confirm the persistence of the prosthesis in the intervention group) in case of suspicion of recurrence / biliary pathology or complication secondary to The technique. In the face-to-face visits, the gastrointestinal quality of life index will be used (in its Spanish version validated by Quintana et al). At the end of the 1-year follow-up, patients belonging to the intervention group who did not present a migration of the prosthesis will be offered a gastroscopy with sedation to check the normoposition of the prosthesis and that stenosis or other macroscopic lesions at the point of implantation.

Sample size

Assuming a proportion of readmissions of biliary cause of 25% in the control group and 7% in the experimental group, with an alpha risk of 5% and a power of 80% and using the arc transformation sine given the proportion of the experimental group, an estimated 60 subjects per group are needed. Given the age of the patients to be included and the mortality associated with the underlying disease, a proportion of losses of 20% is estimated, which would require 75 patients per group. The annual number of ERCP performed at the Río Hortega university hospital ranges from 1,000 to 1100. Assuming also a number of examinations to be carried out in the collaborating centers, with the inclusion and exclusion criteria exposed, a recruitment interval of 12-18 months is estimated.

#### Randomization

It will be done once the patient agrees to participate in the work and has verified the absence of exclusion criteria. To avoid imbalances between the groups, it will be stratified by baseline diagnosis (cholangitis vs others), given that the mortality during admission associated with acute cholangitis is significantly greater than in the rest of the included conditions. Within each stratum a pure randomization will be carried out by means of a sequence generated by computer where the probability of belonging to each group will be 0.5. For each stratum, there will be a total of n numbered closed opaque envelopes (where n = total sample size) that will be stored in the endoscopy unit and will be opened consecutively as participants are included.

#### Masking

To ensure that neither the patients nor the physicians responsible for monitoring and management in the hospitalization facility know the assigned group, transmural biliary drainage placement will not appear in the reports of the endoscopic procedures, which will not include images of the placement. of transmural vesicular drainage. If you have all the information about ERCP. Neither will they have access to the reports or images of the tests carried out during the follow-up specifically to confirm the patency of the drainage.

In case of suspicion of complication, the adverse effects monitoring committee will be notified that, if the suspicion is considered well founded, it will inform about the group and the treatment received by the patient.

To ensure patient safety, a full report will be made available in the databases of the participating centers, so that, in case of any suspicion of serious complication, the detailed information of the procedure can be accessed without the need to wait to the response of the adverse effects monitoring committee.

#### Adverse effects monitoring

The adverse effects identified during the study will be classified according to the classification of ASGE (for adverse endoscopic effects) and CTAE (4th version) for those associated with hospitalization. According to the interval from the procedure they will be divided between postprocedure (in the first 7 days from the same) and late (after this time). Its relationship with the procedure will be classified as definitive, probable, possible or improbable.

An adverse effects committee (constituted by the principal investigator and two investigators not in charge of patient follow-up) will be constituted to notify all the adverse effects identified. The committee will meet twice a month to collect the identified adverse effects. In case of establishing a definitive, probable or possible relationship with the procedure, the endoscopic treatment performed on the physicians responsible for the patient's management will be discovered. If a serious adverse effect is suspected, the treatment received at the time of notification of one of the committee members will be revealed without waiting for the next scheduled meeting.

#### Data Collect

The data collection will be done by the main researcher or collaborating researchers through a data collection notebook (CRD) anonymously and dissociated from the clinical information by means of a patient identification code. From the data collection notebook the information will be transferred to a database made through the RedCap platform, available through the Spanish Association of Gastroenterology. The database will be protected with a password to which only researchers will have access. The data concerning the admission and baseline characteristics will be collected during the first hospital admission. The variables related to the endoscopic intervention will be collected during the same. The variables of follow-up after discharge will be collected either during scheduled visits at 3, 6, 9 and 12 months or if re-admissions occur during these. The economic variables, the costs, will be those offered by the economic management units of each center.

#### 6. Data management

Data from the data collection notebooks will be merged by the main researcher or collaborating researchers anonymously, encrypted and decoupled from the clinical information by means of a patient identification code (ID), in a database made through the application RedCap available through the Spanish Association of Gastroenterology and the data will be downloaded in the form of an Excel file (Microsoft Corporation, Redmond, WA USA). The responsible researcher will define an ID for each participant. The data entered in the database will be anonymous and the database will be protected with a password to which only the researchers will have access.

The unified file will be kept in the Río Hortega University Hospital and will be maintained until the end of the study. Regarding the application of the Organic Law on Data Protection 15/1999 and Royal Decree 1720/2007 that develops it, it should be noted that the protocol defined in the project oriented to epidemiological analysis, determines that the files will record information completely anonymized. A file with the information collected for the development of the project will be maintained within the framework defined in the Security Document of the maximum level of the Río Hortega University Hospital whose responsibility is the Management of said organization. Said document is public, of obligatory knowledge and available in the Intranet of the University Hospital Río Hortega. The levels of security, access and availability will be defined in said document. Said file will be declared within the file of personal data called "Biomedical Research. Biobank".

## 7. Statistical analysis

It will be done through the STATA program (StataCorp, 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

### Descriptive analysis

In the quantitative variables the arithmetic average and the standard deviation will be calculated (the variables that do not follow a normal distribution will be described with median, minimum, maximum and interquartile range), and the categorical ones will be expressed as percentages and their 95% confidence intervals.

### Hypothesis contrast

The analysis of the primary objective, the hospital admission of biliary cause, will be carried out through the Z test of homogeneity without using the correction of Yates. The confidence interval of the difference between the two groups will also be estimated. An intention-to-treat analysis will be performed, regardless of the endoscopic treatment received after randomization. There will also be an analysis per protocol, including only the subjects of each group in which the assigned treatment is carried out successfully. To evaluate possible confounding factors (diagnosis at admission, reference center, severity at admission, age, sex, follow-up center) logistic regression techniques will be performed, using the STATA confound user command that generates all possible combinations. From the possible confounding factors, defining as a significant change that which conditions a change in the hazard ratio greater than 10% with respect to the one obtained with the complete model. In case several models do not present differences greater than 10%, the most parsimonious will be chosen. In case the chosen model only includes a categorical variable, the relative risk stratified by that variable will be offered.

Given that there may be differences in time to recurrence in both groups, we will also assess the occurrence of recurrences using Cox risk regression models. Patients will be censored at the time of loss of follow-up or death due to non-biliary causes. Any urgent admission due to biliary complications will be considered as a relapse. To avoid bias, a sensitivity analysis will be carried out including hospital admissions for any reason, to avoid possible errors when cataloging the main diagnosis of admission. To evaluate possible confounding factors (initial symptoms, age, sex, biliary prosthesis ...) the STATA confound user command will be used, defining as a significant change that which determines a change in the hazard ratio greater than 10% with respect to the obtained with the complete model. In case several models do not present differences greater than 10%, the most parsimonious will be chosen.

Within the secondary objectives, the costs in both groups will be compared using the student's t-test the variables "index admission cost" and "total hospital costs". The proportion of complications in both groups will be analyzed as dichotomous depending on their appearance (if the patient has at least one event defined as a complication) and, depending on the severity (proportion of patients with serious complications, defined as a grade 3 or higher according to the CTCAE). According to the proportions, the Z test or the Fisher exact test will be used.

To evaluate the number of readmissions (biliary and for any reason) during the 1-year follow-up, negative binomial regression techniques will be used. Depending on the number of null values (patients without any re-entry during follow-up) it may be necessary to use a negative binomial regression model with inflated zeros. In this case, patients will be censored only in case of death, loss or end of follow-up.

## 8. Ethical aspects

### 8.1 Benefit-risk assessment for research subjects

The benefit we are looking for is to significantly reduce the risk of re-admission due to biliary pathology in patients not subsidiary of surgical treatment with symptomatic choledocholithiasis. Currently approximately 25% of the elderly who do not undergo a cholecystectomy present a re-entry in the first year of follow-up and, according to the available data, we estimate that the placement of an internal vesicular drainage would reduce it below 10%. It must be borne in mind that the mortality of these recurrences may vary between 5-10% of patients. When performing vesicular drainage at the same time as ERCP, it is not necessary to subject the patient to a new sedation. The placement of a transmural vesicular drainage is not exempt from risks. In the series published, the proportion of patients with serious complications ranges between 5-10% and include bleeding, migration of the prosthesis or bile leak. The proportion of patients with complications requiring urgent reoperation is 2%.

## 8.2. Confidentiality of the data

The data of the study will be initially dissociated from the identity of the participant, through an ID, by the responsible physician. The relationship between the ID and the identity of the participant will be guarded by the investigating doctors in a file protected with a personal password. The data will be entered into the database anonymously with the participant ID, to maintain its anonymity. The database will be protected by means of a password, and only accessible by researchers. During the study, strict compliance with Law 15/1999, of December 13, Protection of Personal Data is guaranteed.

## 9. Schedule and dissemination plan of the study

First year

Recruitment of patients. Patient tracking

Second year

Recruitment of patients (first half). Patient tracking

Third year

Patient follow-up (first half). Data analysis. Presentation at scientific meetings.  
Publication of the results.