

**ENDOSCOPIC SPHINCTEROTOMY WITH BALLOON
DILATATION VERSUS SPHINCTEROTOMY ALONE
FOR COMMON BILE DUCT STONES REMOVAL**

BY

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DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS
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ABSTRAK

Laterbelakang dan Objektif: Sfinkterotomi endoskopik dengan pelebaran papilla menggunakan belon (EST+ EPLBD) adalah satu kaedah alternatif selain daripada sfinkterotomi endoskopik sahaja (EST sahaja) untuk membuang batu dalam saluran hempedu umum. Kajian ini bertujuan untuk memandingkan keberkesanan dan keselamatan antara kedua-dua kaedah ini di Hospital Universiti Sains Malaysia (HUSM).

Reka bentuk dan kaedah kajian: Kajian ini dijalankan secara prospektif, di pusat tunggal dan dipilih secara rambang, tanpa pengetahuan pesakit di HUSM. Matlamat utama kajian ini adalah untuk memandingkan keberkesanan dan keselamatan antara kedua-dua kaedah ini. Manakala matlamat sekunder adalah untuk memandingkan tempoh masa dan kadar penggunaan alat tambahan antara dua kaedah ini. Data dianalisis dengan menggunakan “independent sample t-test” dan “Chi2 test”.

Keputusan: Seramai 66 orang pesakit yang menjalani endoscopic retrograde cholangiopancreatography (ERCP) untuk batu dalam saluran hempedu umum yang memenuhi kriteria kemasukan dan tidak ada kriteria pengecualian telah dipilih untuk menyertai kajian ini. Tiga puluh empat orang pesakit berada dalam kumpulan EST+ EPLBD($n=34$) dan 32 orang lagi pesakit dalam kumpulan EST sahaja($n=32$). Pesakit yang daripada kumpulan EST sahaja yang gagal mencapai sepenuh pembuangan batu dalam saluran hempedu umum akan ditukar kepada kumpulan EST+EPLBD dengan tujuan untuk merawat dan membuang batu dalam saluran hempedu umum dengan sepenuhnya. Kadar pembuangan batu dalam saluran hempedu umum bagi dua kaedah ini adalah setara (EST+ EPLBD: 100% vs EST sahaja: 93.8%; $p=0.139$). Dua pesakit daripada kumpulan EST(6.2%) sahaja yang gagal mencapai pembuangan sepenuh batu dalam saluran hempedu umum ditukar kepada kumpulan EST+EPLBD dengan niat untuk merawat dan berjaya mencapai pembuangan batu sepenuh. Dua kaedah ini mencapai

masa prosedur yang setara (EST + EPLDB: 15.8 minutes vs EST sahaja: 15.5 minutes; $p=0.860$). Komplikasi prosedur iaitu pankreatitis berlaku pada seorang pesakit di kumpulan EST+ EPLBD (EST + EPLDB: 2.9 % dan EST sahaja: 0 %; $p=0.328$). Manakala, komplikasi prosedur iaitu pendarahan berlaku pada seorang pesakit di kumpulan EST sahaja (EST + EPLDB: 0 % vs EST alone: 3.1 %; $p=0.299$), tetapi tidak ada perbezaan yang ketara antara dua kumpulan ini. Komplikasi prosedur yang lain iaitu saluran bocor dan kolangitis tidak berlaku pada pesakit antara dua kumpulan ini. Tiada penggunaan alatan tambahan dalam kedua-dua kumpulan di kajian ini.

Kesimpulan: Kedua-dua kaedah ini (EST+ EPLBD dan EST sahaja) adalah sama berkesan dan selamat selain mempunyai tempoh masa prosedur yang setara. Walaupun kedua-dua kaedah ini adalah sama berkesan, tetapi, EST+ EPLBD adalah patut digunakan apabila pembuangan batu dalam saluran hempedu umum tak dapat dicapai sepenuhnya dengan kaedah EST sahaja.

ABSTRACT

Background and objective: Endoscopic sphincterotomy (EST) plus endoscopic papillary large balloon dilatation (EPLBD) have been reported as a valid alternative to EST alone in removing common bile duct (CBD) stone. Our aim of this study is to compare efficacy, and safety of these two groups of patients in removing CBD stone in Hospital Universiti Sains Malaysia (HUSM).

Study design and method: This is a prospective single centre randomized single blinded comparative study conducted in HUSM. The primary endpoints for this study are the overall complete stone clearance rate and complication rate, while the secondary outcome for this study are duration of procedure and rate of usage of adjunct. Objective data analysis is conducted using independent sample t-test and Chi2 test.

Result: A total of 66 patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) for choledocholithiasis in which is CBD stone who fulfilled inclusion criteria and has no exclusion criteria are recruited in this study. Thirty four patients were allocated to EST plus EPLBD arm (n=34), and 32 patients were in EST alone arm (n=32) using randomization method. For intention to treat, patient from EST alone arm that unable to achieve complete stone clearance will be switched to EST plus EPLBD arm. The overall complete stone removal rate for both groups were comparable (EST plus EPLDB: 100% versus EST alone: 93.8%; $p=0.139$). The two patients from EST alone group (6.2%) that unable to achieve complete stone clearance were converted to EST plus EPLBD group for intention to treat and able to achieve complete stone clearance by EST plus EPLBD. For procedural time, both arms are comparable as well (EST plus EPLDB: 15.8 minutes versus EST alone: 15.5 minutes; $p=0.860$). Complications such pancreatitis, happened in one patient in EST plus EPLBD arm (EST plus EPLDB: 2.9 % versus EST alone: 0 %; $p=0.328$), and bleeding happened in one patient in EST

alone arm (EST plus EPLDB: 0 % versus EST alone: 3.1 %; $p= 0.299$), but it is not statistically significant. No perforation or cholangitis complication happened in both groups. No adjunct usage in both groups as well.

Conclusion: Both EST plus EPLBD and EST alone are equally effective, safe and has comparable procedural time in removing CBD stone. Even though both methods are equally effective, EPLBD plus EST is considered as a solution if complete stone clearance unable to achieve via EST alone.

1.0 INTRODUCTION

1.1 INTRODUCTION AND LITERATURE REVIEW

Gallstone is a worldwide clinical problem which affecting most of the populations with incidence of 15 to 20% in west and 10% in Asians.¹ About 5 to 15% of patient with gallstone will go on to develop bile duct calculi.² Complication of common of bile duct stone can be devastating including pain, complete or partial biliary obstruction leading to obstructive jaundice, cholangitis, hepatic abscess, pancreatitis, and secondary biliary cirrhosis.³ Thus, due to these serious complications, there are several endoscopic strategies developed for treatment of common bile duct stone.

Endoscopic sphincterotomy (EST) was developed in 1974.⁴ It is most commonly used during endoscopic retrograde cholangiopancreatography (ERCP) to remove common bile duct (CBD) stone. It is most frequently used and considered as standard therapy for treatment of choledocholithiasis.

While, in 1983, Staritz developed another method that is endoscopic papillary large balloon dilatation (EPLBD) and it is an alternative to EST in clearing CBD stone.⁵

On the other hand, Ersoz introduced another method called combination of EST plus EPLBD in 2003 as an alternative method to EST alone and EPLB.⁶

Our aim of this study is to compare efficacy, and safety of these two groups in removing CBD stone.

1.2 STUDY RATIONALE

Despite there are many studies done on evaluating efficacy and safety of EST plus EPLBD and EST alone in removing CBD stone, but there is no definite conclusion on superiority of EST plus EPLBD when compared with EST alone in removing CBD stone. There is also lack of local data/study on this topic.

As CBD stone is a global issue and potentially bring devastating complications, we would like to conduct a randomised controlled trial in evaluating the efficacy, feasibility, and safety of EST plus EPLBD versus EST alone in clearing CBD stone.

The conclusion of the study might provide a good alternative method which is EST plus EPLBD to remove CBD stone apart from EST alone in local practice setting.

2.0 STUDY PROTOCOL

2.1 DOCUMENTS SUBMITTED FOR ETHICAL APPROVAL ENDOSCOPIC SPHINCTEROTOMY WITH BALLOON DILATATION VERSUS SPHINCTEROTOMY ALONE FOR COMMON BILE DUCT STONES REMOVAL

Protocol JEPeM Code: USM/JEPeM/21020173

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Introduction and Literature Review

Endoscopic sphincterotomy (EST) is most commonly used during endoscopic retrograde cholangiopancreatography (ERCP) to remove common bile duct (CBD) stone and considered as standard therapy for treatment of choledocholithiasis. However, in view of EST requires an adequate incision on major duodenal papilla to achieve biliary cannulation, it can potentially cause damage to biliary sphincter during the procedure and potentially increased risk of some complications such as bleeding and biliary reflux.⁷ This procedure carries risk of complications such as haemorrhage, perforation, and long-term effect like sphincter dysfunction.⁸

Staritz introduced a method called endoscopic papillary large balloon dilatation (EPLBD) in 1983 as an alternative to EST in clearing CBD stone.⁵ EPLBD can reduced the risk of bleeding and perforation post procedure, but it carries higher risk of post-ERCP pancreatitis.⁹⁻¹¹ However, EPLBD is usually only useful in extracting small to moderate sized stone which is less than 10mm.¹²

About 10 to 15% of CBD stone was unable to extract by both EST or EPLBD alone, especially in those patients with big and difficult stone (size bigger than 10 to 15mm, numerous, barrel-shaped, and impacted stones).¹³ Besides that, other factors that can contribute to failure of stone extraction are periampullary diverticulum or post operative variation, tortuosity and tightening of distal common bile duct.¹⁴

In 2003, Ersoz introduced combination of EST plus EPLBD as an alternative method.⁶ It can reduce the risk of complications through avoiding a complete sphincterotomy, shortening procedural time, and reducing the need of usage of mechanical lithotripsy.¹¹

In a study on 2007, it showed that EST plus EPLBD had comparable efficacy and safety when compared to conventional EST alone and both groups have similar complication rate.¹¹

Besides that, in a recent study in 2020, it also showed that EST plus EPLBD had a comparable efficacy when compared with EST alone in clearing CBD stone and EST plus EPLBD required shorter procedural time when compared with EST alone. There is no significant increased risk in pancreatitis for EST plus EPLBD.¹⁵ While, in a randomized controlled study in 2017, it showed that EST plus EPLBD is more effective than EST alone in clearing large CBD stone and is equally safe compared to EST alone.¹⁶ In another randomized controlled trial in 2013, the study showed that the success rate for complete CBD stone removal in first session is higher in EST plus EPLBD group when compared to EST alone and it is statistically significant. But the overall stone clearance rate and complication rate was similar in both groups.¹⁷ Apart from that, there are many other studies have suggested that EST plus EPBD as a safe and promising alternative to conventional EST or EPLBD.¹⁸⁻²⁰ In a published meta-analysis, accumulated data showed that EST plus EPLBD is a safe and effective procedure in removing large or difficult CBD stone without any additional risk of complications.²¹

There is still no definite conclusion in evaluating superiority of EST plus EPLBD vs EST alone in term of efficacy in removing CBD stone.

Problem statement & Study rationale

Despite there are many studies done on evaluating efficacy and safety of EST plus EPLBD and EST alone in removing CBD stone, but there is no definite conclusion on superiority of EST plus EPLBD when compared with EST alone in removing CBD stone. There is also lack of local data/study on this topic.

As CBD stone is a global issue and potentially bring devastating complications, we would like to conduct a randomised controlled trial in evaluating the efficacy, feasibility, and safety of EST plus EPLBD versus EST alone in clearing CBD stone.

The conclusion of the study might provide a good alternative method which is EST plus EPLBD to remove CBD stone apart from EST alone in local practice setting.

Research Question(s):

- Does EST plus EPLBD have better overall successful clearance rate than EST alone in removing CBD stone?
- Does EST plus EPLBD have shorter time of procedural time than EST alone in removing CBD stone?
- Does EST plus EPLBD bring more complications (bleeding, pancreatitis, cholangitis, perforation) than EST alone in removing CBD stone?

Primary Objective

General: To compare the efficacy and safety of EST plus EPLBD and EST alone in removing CBD stone.

Specific:

- To determine the overall complete stone clearance rate between EST plus EPLBD and with EST alone in removing CBD stone.
- To compare complication rate (bleeding, pancreatitis, cholangitis, perforation) between EST plus EPLBD and EST alone

Secondary outcome

- To determine the duration taken for stone clearance for EST plus EPLBD in comparison with EST alone.
- To compare usage rate of other adjunct (mechanical lithotripter/basket) in removing CBD stone between EST plus EPLBD and EST alone

Research Hypothesis

First Hypothesis

H0: There is no difference in overall stone clearance rate between EST plus EPLBD and EST alone.

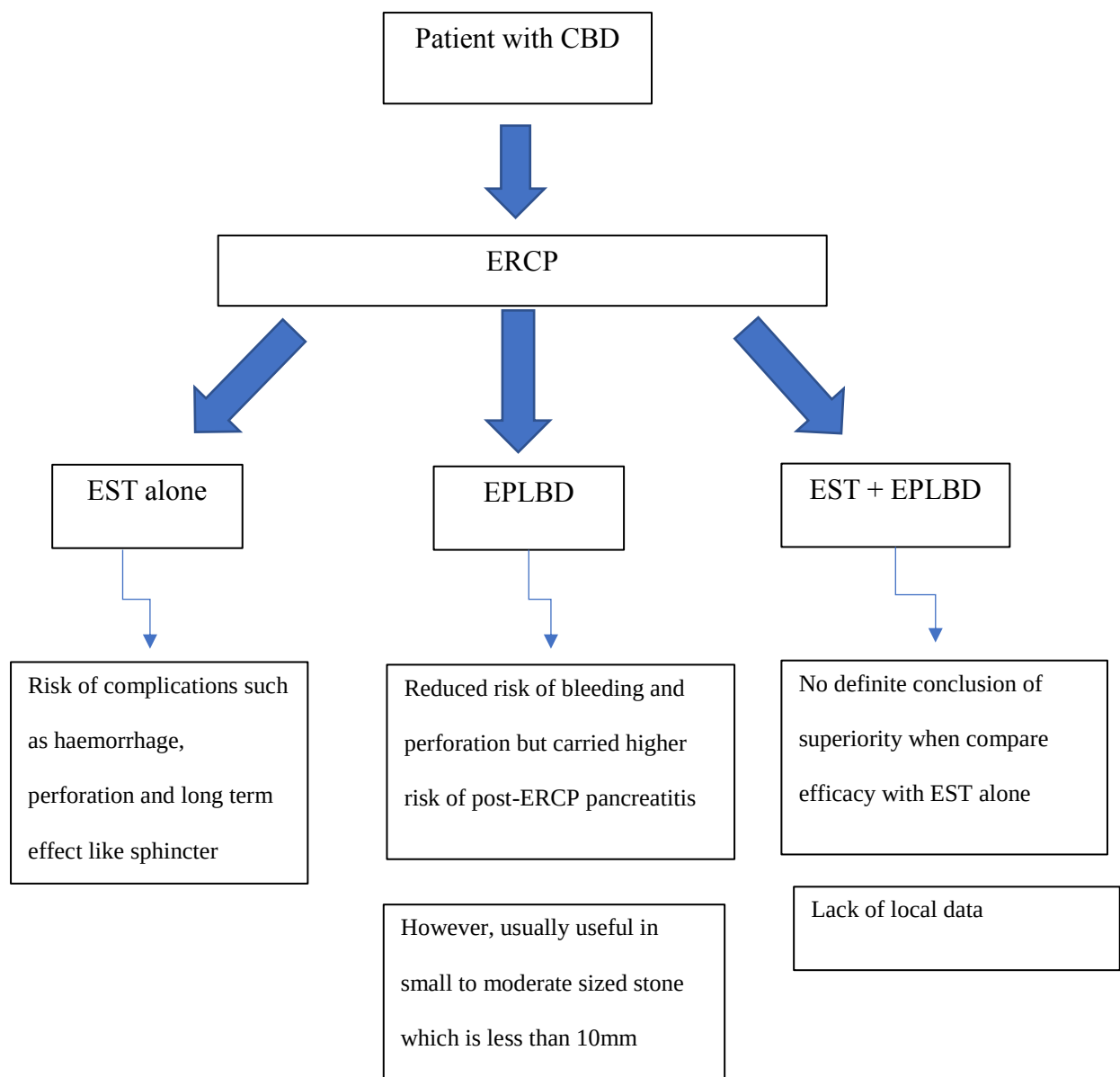
H1: EST plus EPLBD has better overall stone clearance rate than EST alone in removing CBD stone.

Second Hypothesis

H0: There is no difference in complications rate between EST plus EPLBD and EST alone.

H1: EST plus EPLBD has higher complication rate when compared to EST alone in removing CBD stone.

Conceptual framework



Research design

This is a single centre and randomized controlled trial conducted in HUSM.

Patient with CBD stone who seek treatment at HUSM and fulfilled the inclusion criteria and none of the exclusion criteria, will be recruited for the study.

Study area

Endoscopic unit and operation theatre of Hospital USM.

Study population

Reference population – patient with CBD stone

Target population- patient with CBD stone who seek treatment in Hospital USM

Source population/sampling pool - patient with CBD stone who seek treatment in Hospital USM

Sampling frame- patient with CBD stone who seek treatment at HUSM and fulfilled the inclusion criteria and none of the exclusion criteria from 28/6/2021 to 27/6/2022

Subject criteria

Inclusion Criteria

- Patient's age 18 and above
- Patient with CBD stone documented on imaging studies

Exclusion Criteria

- CBD stone size more than 15mm
- More than 3 CBD stones

- Concurrent hepatobiliary tumour
- Intrahepatic stone
- Bleeding tendencies: coagulopathy, thrombocytopenia, patient on anticoagulant medication
- Patient in sepsis/ Cholangitis patient
- Patient with acute pancreatitis
- Prior history of Bilioth II or Roux-en-y surgery

Sample size estimation

Assuming a 22.1% difference in CBD stone clearance rate in one endoscopic session with 74% in conventional group (EST alone) and 96.1% in EST plus EPLBD based on previous positive series by Karsenti in 2017,¹⁶ with the usage of Power and Sample size programme, under Dichotomous test for sample size, Design: Independent, prospective, two proportion study, uncorrected chi-square test, with type 1 error of 0.05 (2-sided) and a power of 80%, P_0 of 0.74, P_1 of 0.961 and $m=1$, the sample size needed is 40 .

Add on 10% dropout : $40 + 4 = 44$ for each arm.

Final sample size = 88

Subject Recruitment

A total of 88 patients with CBD stone which presented to Hospital USM and fulfilled inclusion criteria and none of the exclusion criteria from 28/6/2021 to 27/6/2022, will be recruited to the study.

Based on literature review as above, there are 3 methods used to remove CBD stone via ERCP that are EST alone, EST+EPLBD and EPLBD alone. In our study, only EST alone and

EST+EPLBD will be compared. This is because EPLBD alone is usually only useful in small CBD stone and it carried higher risk for post-ercp pancreatitis.

All the cases will be carried out by one Consultant Hepatobiliary Surgeon, with more than 5 years of experience in the field.

Cholangiogram will be performed in the same setting after procedure to detect any residual stone.

There is possibility of crossover of both arm in this study in which failure to clear all stone in EST alone will be proceeded with EST+EPLBD.

Randomization and Masking

88 patients with CBD stone will be divided into two groups which is Group A(EST+EPLBD) (44 cases) and Group B (EST alone) (44 cases). There will be no stratification or matching of subject from both arm of the study. Randomization will be done using computer software for sequence generation and was applied with 1:1 allocation using random block sizes of 6 and 8 to Group A or Group B. The allocation concealment mechanism was developed by preparing 88 sealed and opaque envelopes. Each envelop contain one allocation sequence which is generated by computer software. Data collection officer will randomly open one of the envelop each time one patient recruited and will need to follow the allocation sequences inside the envelop to determine whether the patient to be Group A or Group B patient. This is single blinded study whereby the participant is blinded but the endoscopist is not blinded.

Research tool

- Data Collection Pro forma

Operational definition

CBD complete stone clearance: no residual stone on cholangiogram in one endoscopic session (either via EST alone or EST plus EPLBD)

Duration of procedure: Defined as the duration of time from starting of intervention (EST alone or EST +EPLBD) until complete stone clearance as evidenced in cholangiogram.

Number of attempts: Defined as number of attempt that conventional retrieval balloon used after intervention done (EST alone or EST +EPLBD) to remove CBD stone.

Post ERCP pancreatitis: Persistent abdominal pain more than 24 hours after ERCP and associated with rise of serum amylase more than three times of the upper normal limit.²²

Haemorrhage: Evidence of bleeding such as melena or hematemesis with drop in at least 2g/dl of haemoglobin concentration or need for a blood transfusion.⁷

Cholangitis: Fever in which temperature > 38-degree Celsius accompanied by leucocytosis and right upper quadrant abdominal pain after the procedure, without concomitant evidence of acute cholecystitis.⁷

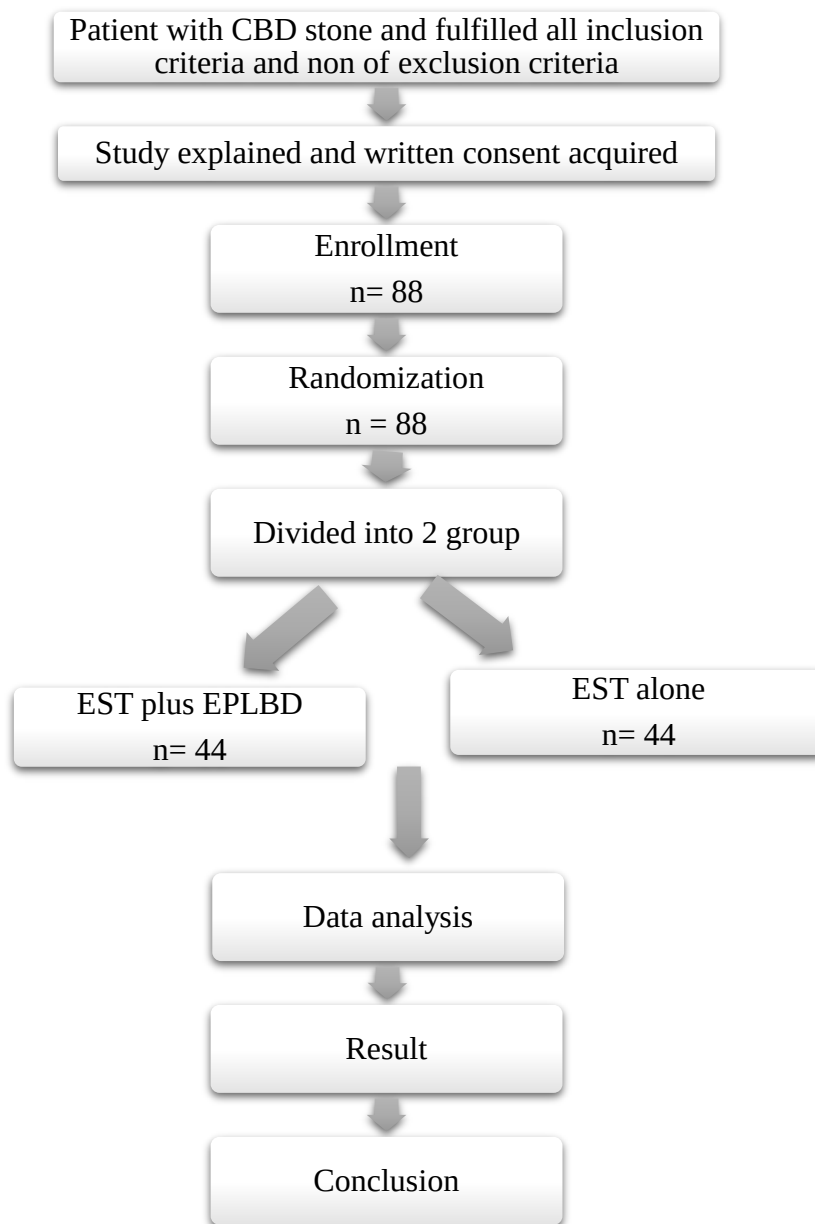
Data collection method

A total of 88 patients with CBD stone who meet all the inclusion criteria and none of the exclusion criteria from period of 28/6/2021 to 27/6/2022, will be recruited to this study. The patient will be explained regarding the study and will be given full freedom to participate or not without affecting her medical condition management and care. Only the patient who is 18 years and above with no impairment in cognitive function will be enrolled in the study. Written consent will be taken if patient decided to participate in this study.

Eighty-eight patients with CBD stone will be divided into two groups which is Group A(EST+EPLBD) (44 cases) and Group B (EST alone) (44 cases). Randomization will be done using computer software for sequence generation and was applied with 1:1 allocation using random block sizes of 6 and 8 to Group A or Group B. The allocation concealment mechanism was developed by preparing 88 sealed and opaque envelopes. Each envelop contain one allocation sequence which is generated by computer software. Data collection officer will randomly open one of the envelop each time one patient recruited and will need to follow the allocation sequences inside the envelop to determine whether the patient to be Group A or Group B patient. This is single blinded study whereby the participant is blinded but the endoscopist is not blinded.

Participant will be admitted 1 day prior to the procedure and will be monitored in ward for at least 1 day after the procedure for any complication post procedure. Total duration of involvement will be at least 72 hours.

Study flowchart



Data analysis

Primary outcomes measured in both groups are the overall stone clearance rate in one endoscopic session and complication rate post procedure. While secondary outcome includes procedural time and usage rate of adjuncts.

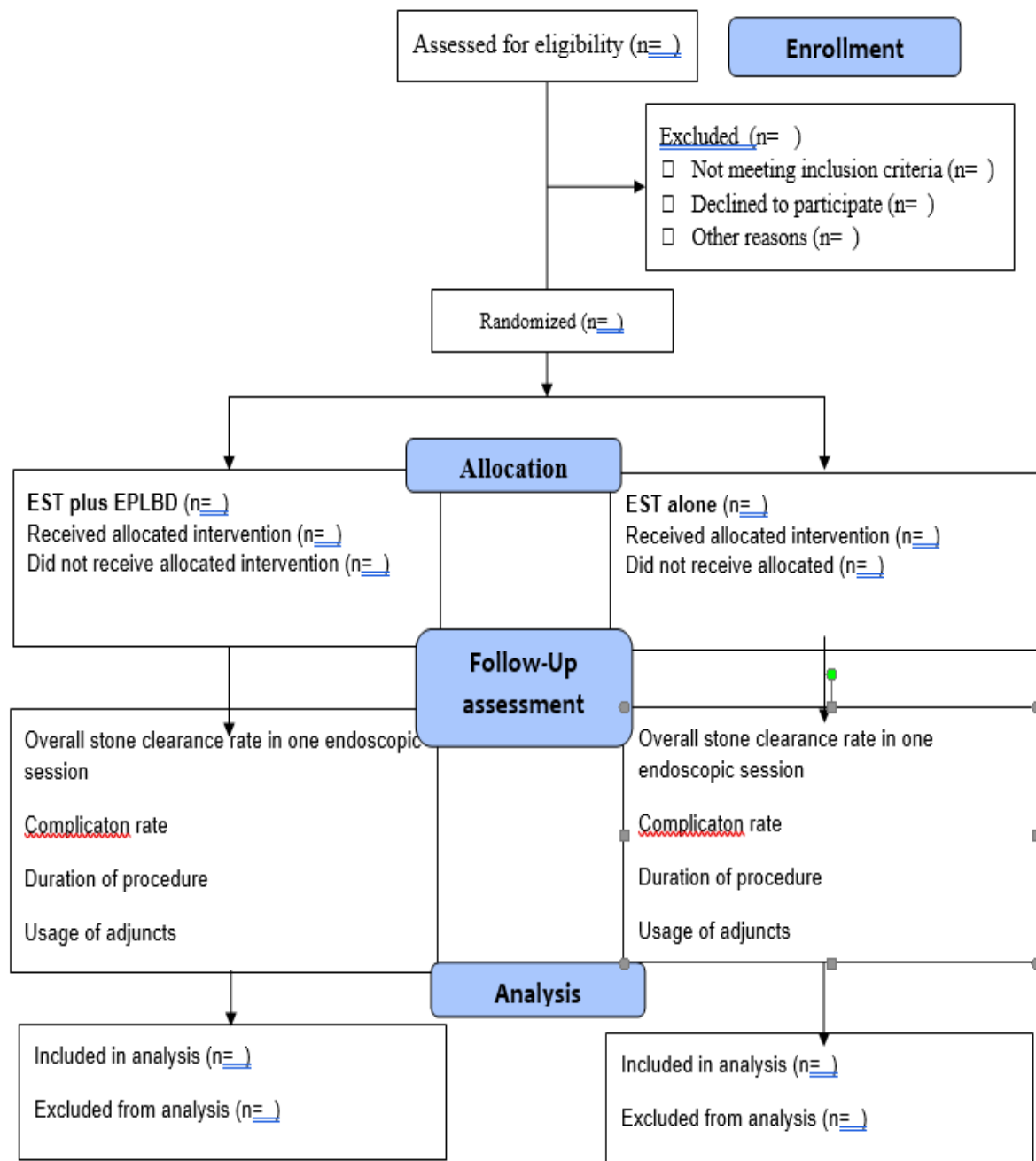
Categorical variables are compared using Chi-square test while continuous variables is compared using student's t-test. All tests are two-sided and p value of < 0.05 is considered statistically significant.

Descriptive statistics will be used to summarise the socio-demographic characteristics of patients.

All Data will be analysed using SPSS for Windows (version 24, SPSS Inc., Chicago, IL, USA).

CONSORT FLOWCHART OF THE STUDY

CONSORT Flow Diagram



Expected Results

Table 1 comparison of baseline characteristics between both study groups

	EST + EPLBD (n=44)	EST alone (n=44)	P-value
Age (years)			
Sex M/F			
Stone number			
Stone size (mm)			
Periampullary diverticulum			
Pre-ERCP lab investigations			
Total bilirubin (µmol/L)			
Direct bilirubin (µmol/L)			
Alkaline phosphatase (ALP)			
Serum albumin (g/dl)			
INR			
Serum amylase			
Serum creatinine level (µmol/L)			
Haemoglobin (g/dl)			
Platelet count (10³ /µL)			
White blood cell count (10³ /µL)			

Table 2 Comparison of the endoscopic and post -ERCP data between both study group

	EST + EPLBD (n=44)	EST alone (n=44)	P-value
Procedure duration (min)			
Precut			
Successful stone extraction			
Post ERCP pancreatitis			
Periampullary diverticulum			
Usage of adjuncts (mechanical lithotripsy/basket)			
Post-ERCP lab investigations			
Total bilirubin (µmol/L)			
Direct bilirubin (µmol/L)			
Serum amylase			
Haemoglobin (g/dl)			

Gantt chart & milestone

Activities	2021										2022									
	Ma rch	Ap ril	Ma y	June2021 until June 2022		July	Aug ust	Sept	Oct	Nov										
Application for ethical approval																				
Application from hospital director																				
Modification of Protocol																				
Data Collection																				
Data entry																				
Analysis of Data																				
Thesis writing																				
Thesis submission (first draft)																				

Correction thesis submission										
Submission of final research										

Budget proposal

Self-funding.

1. Consent form, 2 pages each set.

$2\text{pages} \times 5\text{cent/page} \times 100\text{sets} = \text{RM}10$

2. Proforma of the research, 4 pages each set.

$4\text{ pages} \times 5\text{cent/page} \times 100\text{sets} = \text{RM}20$

3. Miscellaneous, example: additional papers, pens, organising folders, storage box.

Estimation: RM40

Total estimation cost: RM70

Ethical consideration

Approval will be obtained from the Research and Ethics Committee of Universiti Sains Malaysia (USM) before starting the study.

Declaration of conflict of interest

I understand and declare that conflict of interest may arise as I am part of the team looking after, treatment care and managing the patient with CBD stone that presented to Hospital USM. However, patient will be explained and given full freedom to participate or not without affecting or delaying her actual medical management and care. Patient participation in the study will not be stated in the medical record or disclosed to the researcher and other treating team members to avoid potential conflict of interest in the care of the patients.

Privacy and confidentiality

All forms are anonymous and will be entered in SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the responders individually.

Community sensitivities and benefits

The results and outcome from this study can provide a better picture of overall efficacy rate and complications rate for both arms. Thus, it might provide the community a good alternative method which is EST plus EPLBD apart from EST alone in tackling CBD stone.

EST alone is the standard method of ERCP in removing CBD stone. Many studies had proved that both EST alone and EST plus EPLBD is equally safe. Patient will be explained regarding risks of complications that might occurred after the procedure and consent will be taken. Patient will be monitored in ward post procedure.

Honorarium and incentives

There will be no honorarium or incentives offered to those who participate in the study. Likewise, there will be no additional costs to the patient for participating than that of the usual cost of their treatment having not participated.

Subject Vulnerability

On the first arrival to Hospital USM, the patient will be explained regarding the study and will be given full freedom to participate or not without affecting her medical condition management and care. Only the patient who is 18 years and above with no impairment in cognitive function will be enrolled in the study.

Patients with CBD stone will be divided into two groups which is Group A(EST+EPLBD) (44 cases) and Group B (EST alone) (44 cases). Randomization will be done using computer software. Data will be recorded in proforma by data collector/research assistant.

Risks

Post ERCP complications that will be evaluated in this study includes pancreatitis, bleeding, perforation, and cholangitis.

For removal of CBD stone by means of ERCP, EST alone is the most frequent method and it is considered as standard method. For this study, we are comparing between EST alone versus EST plus EPLBD group in removing CBD stone.

In a study in 2007, it showed that both EST alone and EST + EPLBD had similar complication rate whereby there is 4% of patient developed post ERCP pancreatitis for both arm, none of the patient had post procedure bleeding episode for EST plus EPLBD group, while 2% of patient had bleeding episode in EST alone group. But it is not statistically significant.¹¹ In addition, in another study by in 2017, it showed that there is 0.8% of patient developed post ERCP pancreatitis in group of EST plus EPLBD and there is none of the patient developed post ERCP pancreatitis in EST alone group.¹⁶ But it is not statistically significant. In the same study, it showed that there is 4.1 % patient develop bleeding in EST plus EPLBD group , while there is 3.7% patient developed bleeding in EST alone group, but it is not statistically significant. Moreover, there is 1.4% of patient had perforation post

procedure for EST plus EPLBD group, while there is none of patient had perforation post procedure for EST alone group, but it is not statistically significant. In the same study also, none of the patient develop post ERCP cholangitis in both groups. In a recent study in 2020, it showed that 5% of patient undergone EST+EPLBD developed post ERCP pancreatitis, while 10% of patient undergone EST alone developed post ERCP pancreatitis. In the same study, none of the patient developed post procedural bleeding and perforation.¹⁵

In short, both arm of the study is equally safe.

The patient will be monitored in ward post procedure for all these post procedure complications.

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