Comparison of endoscopic ultrasound-guided hepaticogastrostomy and the antegrade technique: study protocol for a prospective, multicentre, randomised controlled trial

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Abstract

Background: Endoscopic ultrasound-guided biliary drainage (EUS-BD) is used after failed endoscopic retrograde cholangiopancreatography. Based on existing studies, intrahepatic (IH) approaches are suggested to be preferred in patients with a dilated IH bile duct. Both ultrasound-guided hepaticogastrostomy (EUS-HGS) and ultrasound-guided antegrade treatment (EUS-AG) are available IH approaches for patients with an unreachable papilla. However, a direct comparison between these two approaches is lacking. Therefore, we aim to evaluate and compare the safety and efficiency of EUS-HGS and EUS-AG in patients with an unreachable papilla.

Methods: This is a prospective, randomised, controlled, multicentre study. One-hundred forty-eight patients from three hospitals who met the inclusion criteria will be randomly assigned (1:1) to undergo either EUS-HGS or EUS-AG for relief of biliary obstruction. The final study follow-up is scheduled at 1 year postoperatively. The primary endpoint is to compare the safety and efficiency of EUS-HGS and EUS-AG in patients with an unreachable papilla. The secondary endpoint is the overall survival rate of patients undergoing EUS-HGS and EUS-AG. The chi-square test, Kaplan-Meier methods, the log-rank test, and Cox regression analysis will be used to analyse the data.

Discussion: To our knowledge, this is the first study to compare these two EUS-BD approaches directly using a multicentre, randomized, controlled trial design. The clinical economic indexes will also be compared, as they may also affect the patient's choice. The result may contribute to establishing a strategic guideline for choosing IH EUS-BD approaches. Trial registration: Chinese Clinical Trial Registry (ChiCTR), ChiCTR1900020737; registered on 15 January 2019.

http://www.chictr.org.cn/showproj.aspx?proj=33672

Background

Obstructive jaundice is the main cause of death due to malignant biliary tumours. However, because of the insidious onset, the detection of cholangiocarcinoma is always too late for surgical resection of the primary tumour. Endoscopic retrograde cholangiopancreatography (ERCP) has been the standard procedure for palliative biliary drainage in patients with both benign and malignant biliary obstruction [1–3]. Nevertheless, there is still a certain failure rate of ERCP because of the difficulty of cannulation

caused by the variant ampullary anatomy [2]. The traditional way of relieving biliary obstruction after failed ERCP is to perform percutaneous transhepatic biliary drainage [1, 3]. This long-term external drainage can cause an electrolyte imbalance, and the persistent pain and repeated infection of abdominal wall fistula can seriously affect patients' quality of life [1]. Therefore, since it was first described in 2001, ultrasound-guided biliary drainage (EUS-BD) is increasingly used as an endoscopic alternative to failed ERCP because of its high success rate, low adverse event rate, and advantage of immediate internal drainage [4–7].

According to the drainage route, EUS-BD can be categorised into transduodenal extrahepatic approaches and transgastric intrahepatic (IH) approaches. With the advantage of a lower bile leakage rate and better retention of the original anatomical structure, the IH approaches are suggested to be the first choice for patients with a dilated IH bile duct after failed ERCP [8, 9]. The IH approaches include the rendezvous technique (RV), ultrasound-guided hepaticogastrostomy (EUS-HGS), and ultrasound-guided antegrade treatment (EUS-AG). Because of the requirement of retrograde stent implantation, RV is not feasible for patients with an inaccessible papilla, whereas hepaticogastrostomy (HGS) and the antegrade technique (AG) are [10, 11]. However, there a consensus on options for biliary access is still lacking [12, 13]. For patients with malignant biliary obstruction, it is a great challenge to tolerant procedures once and experience postoperative complications. Therefore, the development of a strategy for choosing different approaches, e.g. EUS-HGS and EUS-AG, by comparing their safety and efficiency would be meaningful.

To date, several retrospective studies have compared EUS-HGS and EUS-AG, but a well-designed prospective, randomised study with robust data on this topic is lacking. In the present study, we aimed to compare the safety and efficiency of EUS-HGS and EUS-AG in patients with an unreachable papilla by using a prospective, multicentre, randomised, controlled trial.

Methods/design

Ethical statements

The study was approved by the Medical Scientific Research and New Technology Ethics Committee of Shengjing Hospital of China Medical University (approval number: 2018PS525K) on 22 November

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2018. Subsequently, the boards of the two participating hospitals gave permission to conduct the trial. Informed consent will be obtained from each participant or from each participant's legally responsible relative. The trial was registered in the Chinese Clinical Trial Registry (ChiCTR), ChiCTR1900020737 on 15 January 2019.

Patients

In this prospective, randomised, controlled, multicentre study, patients meeting the inclusion criteria from three hospitals, including Shengjing Hospital in China, Institut Paoli Calmettes in France, and The University of Texas MD Anderson Cancer Center in the United States, will be randomly assigned (1:1) to receive EUS-HGS or EUS-AG for relief of biliary obstruction. A flowchart of the study design is shown in Figure 1.

Inclusion criteria

Patients with unresectable malignant biliary obstruction must meet the following inclusion criteria:

1) IH bile duct dilation confirmed by ultrasonography or CT,

2) failed ERCP,

3) anatomical abnormalities (congenital malformations, upper digestive tract surgery, or tumour mass),

4) low level biliary obstruction and pyloric or duodenal obstruction caused by tumours, and

5) informed consent.

Exclusion criteria

Patients with a clear contraindication to endoscopy will be excluded:

1) haemoglobin level ≤8.0 g/dl;

2) coagulopathy (platelet count <50,000/mm^3, international normalised ratio >1.5) or having taken oral anticoagulation agents, such as aspirin or warfarin, in the previous week;

3) severe cardiorespiratory dysfunction;

4) psychiatric disease, drug addiction, or other reason for unreliable follow-up or responses to questionnaires; and

5) other conditions that negatively affect compliance or place the patient at an increased risk, or

otherwise make them unsuitable for participation.

Primary endpoints

The primary endpoint is to compare the safety and efficiency of EUS-HGS and EUS-AG in patients with an unreachable papilla.

Secondary endpoints

The secondary endpoints are as follows:

1) the overall survival rate for patients undergoing EUS-HGS and EUS-AG;

2) technical success rate, clinical remission rate, complication rate, length of hospital stay, and hospitalisation expenses of EUS-HGS; and

3) technical success rate, clinical remission rate, complication rate, length of hospital stay, and hospitalisation expenses of EUS-AG.

Randomisation and interventions

Randomization is based on envelope method and performed by the trial coordinator in Endoscopy Center of Shengjing Hospital of China Medical University. A sealed and opaque envelope without mark will be opened after patient enrolled by a project secretary. Number ranging from 001 to 148 is sealed into envelop and patients with odd numbers will be treated with EUS-AG, whereas those with even numbers will be treated with EUS-HGS. The final result of randomization will be published to the all trail participants after confirmed.

The equipment used will include a linear array echoendoscope (EG3830UT; Pentax, Tokyo, Japan) in combination with an ultrasound scanner (EUB 6500; Hitachi, Tokyo, Japan). A 19-gauge (G) needle (EUS N–19-T; Wilson-Cook Medical, Winston-Salem, NC, USA) will be used for puncture, and a 0.035-inch guidewire (Jagwire; Boston-Scientific, Natick, MA, USA) will be used for guidance. A cystotome (6-French [Fr]; Wilson-Cook Medical) will be used to dilate the tract and create a large fistula. A fully covered metallic stent (Wilson-Cook Medical) or bare metallic stent (Boston-Scientific) will be used for biliary drainage.

The former part of the procedure is the same in both EUS-AG and EUS-HGS. First, the echoendoscope is advanced into the stomach, and the left lateral lobe liver will be scanned. A dilated IH bile duct

close to the gastric wall will be selected as the puncture point. Then, to avoid the blood vessels in the puncture path, the local vasculature will be checked by colour Doppler ultrasonography, and the 19 G ultrasound puncture needle will be advanced into the IH duct. Next, bile aspiration and cholangiography will be performed to further clarify the location of the puncture needle and delineate the dilated biliary tree down to the point of obstruction.

In the AG group, a guidewire will be inserted through the puncture needle and manipulated into the intestine through the ampulla or anastomosis. A temperate fistula between the stomach (or jejunum in patients with total gastrectomy) and the left hepatic duct will be formed by cystectomy. Once the fistula has been dilated, a self-expandable bare metallic stent measuring 6–8 cm long will be deployed into the malignant biliary obstruction in an antegrade fashion.

In the HGS group, a guidewire will be inserted through the needle and placed in the common bile duct. A cystotome will be used to create a fistula, and a fully covered metallic stent will be deployed into the fistula between the stomach (or jejunum in patients with total gastrectomy) and IH bile duct. Sometimes a bare stent will be placed through the covered stent to avoid stent migration.

Finally, all devices will be removed after confirming that the bile flows well through the stent or stricture with a contrast agent. Additionally, to avoid bile leakage into the peritoneum, a 7-Fr nasobiliary catheter will sometimes be placed through the metallic stent for 48 hours. In cases of failed EUS-AG, EUS-HGS will be performed for patients.

A Consolidated Standards of Reporting Trials (CONSORT) checklist for this study is provided in Additional file 1. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is provided in Additional file 2.

Data collection

Patients' basic information including sex, age, race, and diagnosis will be recorded retrospectively. Concerning feasibility and safety, a routine blood examination, hepatic and renal function test, and biochemical test will be performed on the day before the operation. Ultrasonography or upper abdominal computed tomography (CT) will be performed before the operation to confirm IH biliary dilation caused by obstruction.

Patients will undergo examination of their bilirubin levels on day 1 and day 3 postoperatively to evaluate the efficiency of the operations. Upper abdominal CT will be performed postoperatively to clarify the position of the stent. Technical success is defined as successful stent placement, and clinical success is defined as a decrease in the serum bilirubin level to less than 75% of preprocedural values within 30 days after stent placement.

Adverse events at any time will be recorded and classified as post-procedure (up to 14 days) and late (any time after 14 days) and graded according to the American Society for Gastrointestinal Endoscopy lexicon's severity grading system [14].

Additionally, hospitalisation data including length of hospital stay and total hospitalisation expenses will be recorded. The schedule of enrolment, interventions, and assessments is shown in Figure 2.

Follow-up

The final study follow-up is scheduled at 1 year postoperatively and includes evaluation of perioperative mortality and operative complications. Follow-up assessments of the bilirubin level (total bilirubin, conjugated bilirubin, and unconjugated bilirubin) and survival status are scheduled at 1 month, 3 months, 6 months, and 1 year after operation or until death.

Statistical analysis

Sample size calculation

The statistical significance level is set at 5%, power of the test is set as 80%, and randomisation ratio is set as 1:1. Based on previous data, the overall success rate of EUS-HGS is 84.5–100% with complication rates of 19.6–27% [15–18]. As for EUS-AG, the overall success and complication rates are 57–100% and 0–5%, respectively [9, 15, 18–21].Using a standard sample size formula, it was calculated that 74 patients per group will be needed for 148 patients, after accounting for a 10% dropout rate. A provisional deadline for patient recruitment is set in April 2020, but in case the target number of patients has not been met, the recruitment period may be extended to reach the number required (2 × 67 patients) to obtain power of at least 0.8 (80%).

Statistical analysis

The full analysis set (FAS) should be as close as possible to the intention-to-treat set. On the basis of

the FAS, patients assigned to different group would form the per protocol set. The direct deletion method will be used to treat missing data.

Concerning the primary endpoint, efficiency will be described by the success rate, and safety will be described by the adverse event rate; they will be compared between the procedures using the chi-square test. Normally distributed continuous variables, such as the bilirubin level, length of hospital stay, and hospitalisation expenses will be expressed as a mean±standard deviation and compared using the t test. Concerning the secondary endpoint, Kaplan-Meier methods will be used to compute the survival analyses. The log-rank test and Cox regression analysis will be used to compare the prognosis among patients in the HGS and AG groups. Statistical analyses will be performed using SPSS® Statistics (version 25.0; IBM Corp., Armonk, NY, USA). A two-tailed distribution will be used, and statistical significance will be considered as P<0.05.

Discussion

The choice of drainage approach depends on a patient's individual anatomical structure, underlying disease, and location of biliary stricture. Both HGS and AG are applicable to patients undergoing malignant biliary obstruction with an unreachable papilla. Moreover, efficiency and safety are important for such patients, as it is a great challenge for them to tolerate multiple procedures and postoperative complications. Therefore, a comparative evaluation of EUS-HGS and EUS-AG in terms of efficiency and safety for the development of a strategy to choose the appropriate approach is considered meaningful.

Several studies have reported the efficiency and safety of EUS-HGS and EUS-AG. Artifon et al. compared the safety and efficiency of EUS-HGS and ultrasound-guided choledochoduodenostomy (EUS-CDS) in a randomised controlled trial, and reported that the technical success rate, clinical success rate, and incidence of complications of HGS were 96%, 91%, and 20%, respectively [17]. Uemura et al. systematically searched the literature up to April 8, 2017, and compared the technical success rate, clinical success rate, and incidence of complications of EUS-CDS and EUS-HGS in a systematic evaluation and meta-analysis. The corresponding values for EUS-HGS in that study were 93.7%, 84.5%, and 18.8%, respectively [16]. In a prospective cohort study, Do Hyun et al. proposed

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that the success rate of EUS-HGS was 89%, incidence of complications was 1/8, and success rate of EUS-AG was 57%. In their study, no patient in the EUS-AG group experience postoperative complications [18]. Iwashita et al. reported that the overall success rate and incidence of complications of EUS-AG were 77% and 5%, respectively, by directly adding the number of cases reported in each searched literature [15]. Contrary to other previous reports, Ardengh et al. reported that the success rates of EUS-HGS and EUS-AG were 83.3% and 100%, respectively, by reviewing the different EUS-BD approaches in two hospitals [9]. According to most current studies, the success rate and complication rate of EUS-AG are both lower than those of EUS-HGS. This may be because the operation of EUS-AG is more complex and no permanent fistula or change of anatomical structure is performed [7]. However, the stent in EUS-AG is placed through the tumour, and the growth of the tumour is the main cause of stent re-obstruction. Since a perforating fistula is absent, another intervention for postoperative obstruction will be more difficult in EUS-AG than in EUS-HGS [22]. EUS-HGS may result in more pneumoperitoneum and bile leaks because the fistula traverses the peritoneum [10]. Intraperitoneal deployment is also a potential adverse event of EUS-HGS, which can be fatal [23, 24].

Until now, all existing reports of the safety and efficiency of EUS-HGS and EUS-AG were based on observational studies and randomised controlled studies with another technology or evidence-based medicine. Ardengh et al.'s contradictory findings also appeal to the need for a further comparative study of EUS-HGS and EUS-AG. To our knowledge, this is the first study to compare these two EUS-BD approaches directly in a multicentre, randomised, controlled trial. The clinical economic indexes will also be compared, as they may also affect the patient's choice.

There are limitations to the present study design. The internal biliary drainage operation is a palliative treatment for unresectable malignant biliary obstruction. The lifetime of patients included is limited since death caused by cancer progression is inevitable. Therefore, the long patency of the stent is difficult to evaluate.

Trial Status

The protocol version number is Ver1.3, which was registered on 15 January

2019（ChiCTR1900020737）. Patient enrolment began on 1 July 2019 and completion is expected by 30 April 2020.

Abbreviations

ERCP, endoscopic retrograde cholangiopancreatography; EUS-BD, ultrasound-guided biliary drainage; IH, intrahepatic; RV, rendezvous technique; EUS-HGS, ultrasound-guided hepaticogastrostomy; EUS-AG, ultrasound-guided antegrade technique; HGS, hepaticogastrostomy; AG, antegrade technique; ChiCTR, Chinese Clinical Trial Registry; Fr, French; G, gauge; CT, computed tomography; FAS, full analysis set; EUS-CDS, ultrasound-guided choledochoduodenostomy

Declarations

Ethics approval and consent to participate

Central ethical approval has been obtained from the Medical Scientific Research and New Technology Ethics Committee of Shengjing Hospital of China Medical University (approval number: 2018PS525K) on 22 November 2018. We will not begin recruiting at other centres in the trial until local ethical approval has been obtained. Informed consent will be obtained from each participant or from each participant's legally responsible relative.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Authors' contributions

JT* and SS* conceived the study and prepared a draft manuscript. YL, JT*, SS, SW and XL participated in the design of the study. YL and TX participated in writing the manuscript. SS* approved the protocol. All authors contributed to the study design and commented on the manuscript. All authors read and approved the final manuscript.

Acknowledgments

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Figures

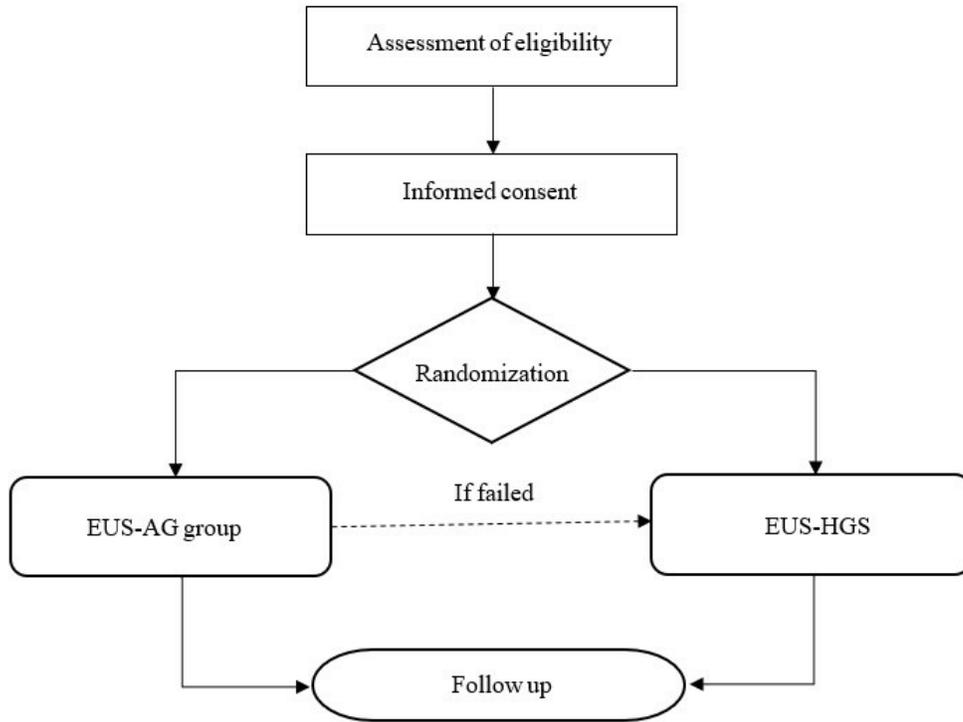Figure 1

A flowchart of the study design.

Time point	Entry	Day of operation	1 day after operation	3 days after operation	1 month after operation	3 months after operation	6 months after operation	Close out: 1 year after operation
					Screening Period			
Inclusion/Exclusion criteria	×							
Informed consent	×							
Basic information	×							
Ultrasonography/Upper abdominal CT	×			×				
Blood routine tests	×		×					
Coagulation routine tests	×							
Blood bilirubin tests — Total bilirubin	×		×	×	×	×	×	×
Blood bilirubin tests — Conjugated bilirubin	×		×	×	×	×	×	×
Blood bilirubin tests — unconjugated bilirubin	×		×	×	×	×	×	×
Operation — AG group		×						
Operation — HGS group		×						
Adverse event — Postoperation complications			×	×				
Adverse event — Late adverse event					×	×	×	×
Length of hospital stay				×				
Total hospitalization expenses				×				
Overall survival rate					×	×	×	×

Figure 2

The schedule of enrolment, interventions, and assessments.

Supplementary Files

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CONSORT Checklist.doc

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