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Study Protocol for Preoperative Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to Main Pancreatic Duct: a multicenter randomized Clinical Trial

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Keywords:	Pancreatic surgery < SURGERY, Pancreatic disease < GASTROENTEROLOGY, Endocrine tumours < ONCOLOGY

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	6
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	10

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	4
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	3
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	6
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	5
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	5
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	5
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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Study Protocol for Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct: a multicenter randomized Clinical Trial in Chinese Tertiary Medical Centers

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Study Protocol for Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct: a multicenter randomized Clinical Trial in Chinese Tertiary Medical Centers

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Abstract

Introduction
The surgical intervention approach to insulinomas in proximity to the main pancreatic duct remains controversial. Standard pancreatic resection is recommended by several guidelines; however, enucleation (EN) still attracts surgeons with less risk of late exocrine/endocrine insufficiency, despite a higher postoperative pancreatic fistula (POPF) rate. Recently, the efficacy and safety of preoperative pancreatic stents placement before the enucleation have been demonstrated. Thus, a multicenter open-label study is being conducted to evaluate the efficacy and safety of stents placement in improving the outcome of enucleation of insulinomas in proximity to the main pancreatic duct.

Methods and analysis
This is a prospective, randomized, open-label, superiority clinical trial conducted at multiple tertiary centers in China. The major eligibility criteria is the presence of insulinoma located in the head and neck of the pancreas in proximity(≤2mm) to the main pancreatic duct. Blocked randomization will be performed to allocate patients into the Stent EN group and the Direct EN group. Patients in the Stent EN group will go through stent placement by the endoscopist within 24 hours before the enucleation surgery, whereas other patients will receive enucleation surgery directly. The primary outcome is the assessment of the superiority of stent placement in reducing POPF rate measured by the International Study Group of Pancreatic Surgery (ISGPS) standard. Both interventions are performed in an inpatient setting and regular follow-up will be performed. The primary outcome (POPF rate) will be tested for superiority with the Chi-square test. The difference in secondary outcomes among the two groups will be analysed using appropriate tests.

Ethics and dissemination
The study was approved by the Peking Union Medical College Hospital Institutional Review Board (K23C0195). Results of the study will be published in an international peer-reviewed journal.

Trial registration number
ClinicalTrials. gov Registry (NCT05523778).

Keywords: Insulinoma, pancreatic duct stent, enucleation, postoperative pancreatic fistula

Article Summary

Strengths and limitations of this study

- A prospective multicenter clinical design to assess the efficacy and safety of a preventive intervention in improving the outcome of enucleation surgery.
- Recruiting patients from multiple tertiary medical centers across China.
- Local online communication tool exploited to promote interactions between investigators and patients

- The lack of blinding of the patients, surgeons, data collectors, and data analysts is the limitation of the study.

Introduction

Insulinomas are the most common functioning pancreatic neuroendocrine neoplasms, with an estimated incidence of 1–4 per million per year [1, 2] They are insulin-secreting tumors that cause common clinical features including neuroglycopenia and autonomic nervous system disorders caused by dysregulated secretion of insulin[3-5]. Surgical management remains the only curative modality for 90% of benign, localized insulinomas[4, 6].

According to several guidelines including the National Comprehensive Cancer Network (NCCN) and the European Neuroendocrine Tumor Society (ENETs)[7, 8], enucleation(EN), a parenchymal preserving modality, that could reduce the risk of late exocrine/endocrine insufficiency, should be considered as the first-line surgical approach for exophytic and peripheral insulinomas[9].

However, in cases of endophytic insulinomas or tumors in proximity to the main pancreatic duct (MPD), the optimal choice of surgical intervention is controversial. Standard pancreatic resection, such as pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), is indicated in guidelines while they aggressively eliminate normal pancreatic tissue, which can lead to long-term consequences including exocrine and endocrine pancreatic insufficiency [10, 11]. Recently, duodenum-preserving pancreatic head resection (DPPHR) was alternatively recommended for the resection of large PNETS.[12] In contrast, performing EN in cases with endophytic insulinomas and tumors in proximity to the MPD still baffles many surgeons as several retrospective researches suggested a significantly elevated rate of post-operative morbidity, especially postoperative pancreatic

fistula(POPF). Lu et.al compared post-operative morbidity between PD and EN, indicating a significant difference in POPF (18.1% vs 61.1%) between the two approaches[13], and Heeger K et al. reported the POPF rate as 70% (21 of 30 patients) after EN of pancreatic tumors located ≤ 3 mm from the MPD [14]. Another study involving 52 patients who underwent EN also demonstrated a high POPF rate of 60% in the group of tumors located at less than or equal to 2 mm from the MPD.[15]. Recently, Dokmak et.al suggested the proximity to MPD < 3 mm as an independent risk factor of POPF in enucleation[16]. Therefore, preventive measures in EN that decrease the POPF rate would encourage the implementation of EN thus improving the long-term benefits for patients with insulinomas in proximity to the MPD.

POPF is usually derived from intraoperative injuries to MPD. Prophylactic preoperative stenting is believed to prevent the MPD injury in that it not only helps to identify the location of MPD in the surgical field thus preventing intraoperative damage but also decompresses pancreatic duct by reducing pancreatic juice leakage from the resection plane and providing support to the duct when stricture develops. Pertinent clinical evidence involving stenting and EN is still lacking. Some researchers reported the usage of preoperative stenting as a prophylaxis for EN[17-21], and despite they all revealed the feasibility and safety of the technique, most of these researches involved a limited number of patients and were single-armed studies.

Based on the knowledge and shortcomings on this topic, our team has collected 18 patients undergoing preoperative stenting in our center for 5 years. We retrospectively analyzed the risk factor of postoperative complications, especially POPF, and discovered

that the distance from insulinoma to MPD ≤2 mm was an independent risk factor for POPF (OR =6.011, p = 0.003). In addition, the preoperative pancreatic stent substantially reduced the incidence of POPF in patients with tumors located in proximity to the MPD (37.5% vs 71.4%, p = 0.028) [22]. Therefore, we launched the current clinical trial to assess the efficacy and safety of preoperative stenting before EN of insulinoma in the head and neck of the pancreas in proximity to the MPD. According to the Evidence Map of Pancreatic Surgery (www.evidencemap.surgery), this is the first trial of its kind[23].

Methods and analysis

➢ Study setting

This is a multicenter, double-arm, prospective, randomized trial in five high-volume medical centers in China. Experienced surgeons will determine the eligibility of their patients and obtain informed consent forms. Eligible patients with insulinoma in proximity to the MPD (≤2mm) will be allocated randomly into two groups: Stented EN group, where the pancreatic duct stents are placed in patients by endoscopist within 24 hours before the enucleation surgery, and Direct EN group, where patients receive direct enucleation surgery. An overview of the protocol is shown in Figure 1. The study started in February 2023 and was planned to finish patient recruitment in December 2025.

➢ Endpoints

Primary endpoint: Rate of POPF within 3 months after EN.

Secondary endpoints:

1) Rate of post-stent-placement acute pancreatitis in Stented EN group within in 3 weeks after EN

2) Operation time

3) Intraoperative blood loss

4) Rate of postoperative abdominal infection within 3 weeks after EN

5) Rate of postpancreatectomy hemorrhage(PPH) within 3 weeks after EN

6) Rate of postoperative lung infection within 3 weeks after EN

7) Rate of postoperative delayed gastric emptying within 3 weeks after EN

8) Rate of postoperative dyspepsia within 6 months after EN

9) Rate of postoperative hyperglycemia within 6 months after EN

10) Total cost of hospitalization

- Definition

In this study, POPF, delayed gastric emptying and PPH adopt the definition proposed by the international pancreatic surgery research group (ISGPS) [24-26]. Pancreatitis, abdominal infection, dyspepsia, lung infection, and hyperglycemia will be evaluated based on Common Terminology Criteria for Adverse Event (CTCAE) V.5.0. Severe adverse events are defined as grade 3 or higher in CTCAE.

- Patients eligibility

Inclusion and exclusion criteria are shown in Box 1

- Randomization

Randomization will be initiated by authorized investigators of the trial after checking the informed consent and the inclusion and exclusion criteria. Each eligible patient will be allocated an individual code/randomization number, which has to be recorded in case report form (CRF). Blocked randomization (blocked number=4) for each center will be

performed using SAS Studio by the study assistant prior to the beginning of enrollment. After randomization, surgeons in all centers who enroll the patient will be informed of the intervention assignment.

➢ Blindness

In accordance with recent academic recommendations on the implementation of blinding in surgical trials[27], meticulous consideration has been given to blinding strategies tailored to distinct study contributors, which encompass patients, surgeons, data collectors, data analysts, and outcome assessors. Patients participating in this study are deemed unblindable due to the number of patients with POPF was 6 (37.5%) and 20 (71.4%), respectively. According to the abovementioned POPF rate in two condition the intrinsic procedural difference between the two groups. Surgeons, who possess a direct line of sight to the presence of the stent during intraoperative procedures, are similarly unfeasible candidates for blinding. Data collectors also find themselves in a position where blinding is not viable, primarily due to the inevitable nature of their responsibilities, which involve the encounter of specific clinical data and records which are integral to prompt group allocation results. Examples of such records are operation records of stenting procedures and diagnostic CT imaging, which may conclusively reveal the presence of a stent within MPD. Furthermore, the integrity of data analysis relies on the unobstructed knowledge of group allocation results, rendering the blinding of data analysts unviable. Recognizing the critical importance of blinding in assessing primary and secondary endpoints, especially those related to complications, outcome assessors are kept blinded to participant group allocation. Based on our protocol, the assessment of endpoints is directly linked with

objective clinical data which can be provided to independent assessors with blindness of allocation. This strategy plays a pivotal role in reducing potential bias in the assessment of primary and secondary outcomes while concurrently insulating the operating surgeon from subjective judgment regarding clinical endpoints. Emergency unblinding is not deemed necessary.

➢ Study interventions

After baseline visit and admission, eligible participants are randomized to the stented EN group or the direct EN group, as shown in Figure 1.

■ Preoperative MPD stenting

The preoperative pancreatic duct stent was regarded as a possible effective method to prevent POPF. The single-pigtail pancreatic duct stent is usually placed within 24 hours before the enucleation endoscopically. The stent length should span the site of the tumor. The length and the diameter of the stent used should be recorded in CRF. The stent was removed by duodenoscopy about three months after surgery. Endoscopic stent placement and removal represents a common procedure at the Endoscopic Center of Peking Union Medical College Hospital and other centers and will be carried out by experienced endoscopists (minimum of 50 procedures) for the study. Any adverse events should be recorded in CRF including stent-related pancreatitis. Blood amylase is tested 2-4 hours after stenting before enucleation to discover potential stenting-related acute pancreatitis.

■ Enucleation

During the surgery, intraoperative ultrasound will be performed to evaluate the location of the tumor and the distance between the tumor and MPD. The peripheral pancreatic lobule

covering the tumor will be exposed by the ultrasound scalpel. After exposure of the insulinoma, the surgeon sutures the lesion and suspends it, and then the insulinoma is dissected from the normal pancreatic tissue. Dissection was performed in contact with the lesion by a combination of harmonic scalpel and bipolar cautery. Frozen sections of resected specimens are regularly investigated to identify benign insulinomas. The operative field should be carefully examined and MPD disruption should be repaired immediately once detected. The prophylactic abdominal drainage tube is applied. Intraoperative conversion (to open procedure, DPPHR, or PD), surgery time, blood loss, and transfusion volume should be recorded in CRF.

- Postoperative management

General clinical treatment and PF prevention treatment will be conducted in both two groups. The patient's body temperature and drainage volume were recorded daily. The amount and the amylase concentration of the drainage fluid as well as the blood was routinely measured on the 1st, 3rd, 5th, and 7th postoperative days. Extubation would be considered if the drainage volume is less than 10 ml for 3 consecutive days or the amylase level of the drainage solution is less than three times the upper limit of normal. If the drainage tube has not been removed at the time of discharge, the patient would be instructed to record the daily drainage until extubation in the outpatient setting.

- Follow-up

For the first three months after discharge, patients should maintain a regular follow-up session for every two weeks through outpatient or telephone. The following information should be collected during each follow-up: basic information and general condition of the

patient, whether the patient has been extubated (if not extubated, record the recent drainage condition), recent medical interventions, and possible manifestations of dyspepsia or hyperglycemia. Laboratory tests and imaging examinations will be done at the surgeon's discretion.

- Statistical methods
  - Hypothesis
    - Null hypothesis

The rate of POPF in patients who undergo MPD stent placement before enucleation is not less than that of patients who undergo enucleation directly.

    - Alternative hypothesis

The rate of POPF in patients who undergo MPD stent placement before enucleation is less than that of patients who undergo enucleation directly.

  - Sample size calculation

In our previous retrospective study, a total of 44 patients with insulinoma in proximity to the MPD who underwent enucleation were included, of which 16 had stent placement and 28 had no stent placement, ands, 38 evaluable patients per group will provide 85% power to reject the null hypothesis in a Z test(unpooled) for superiority at a one-sided significance level of 0.05 considering the POPF rate difference of at least 5% to represent a clinically relevant difference. Therefore, 78 patients in total are to be recruited in the study considering possible dropout.

  - Statistical analysis

The primary outcome (rate of POPF) will be tested for superiority with a Chi-square test assuming a superiority difference of 5% with a one-sided significance level of 0.05. All patients undergoing EN will be included. The analysis will be performed twice: firstly after about 50% of the patients have been discharged and secondly after all patients have finished the follow-up procedure. Secondary outcomes will be described by calculating means or relative frequencies for each treatment group with 95% CIs. Differences in secondary outcomes between two groups will be analyzed using appropriate tests (Shapiro-Wilk tests, t-tests, Mann-Whitney U tests, Wilcoxon rank-sum tests, Chi-square tests, Fisher's exact tests, etc.).

Ethics and dissemination

Written informed consent from all the patients screened will be obtained before the procedures start. The study protocol has been approved by the Peking Union Medical College Hospital Institutional Review Board(approval number K23C0195) and registered in ClinicalTrials.gov(NCT05523778). The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki[28]. Throughout the study, all data acquired in this trial will be provided to the involved investigators and ethics committee members for monitoring, audits, and inspections. Results will be published in an international peer-reviewed journal.

- Patient and public involvement

Throughout the study, a study account based on a local online communication tool (WeChat) will be established to receive any suggestions and consultations from patients

involved and information about the study will be updated for all patients who subscribed to the study account.

Discussion

Generally, enucleation is preferred over other operation approaches in treating insulinomas, as it circumvents complicated reconstructions and possible subsequent complications. However, POPF is common in the enucleation of insulinomas that are in proximal to MPD, which limits its clinical application. In this clinical trial, we aim to demonstrate the safety and efficacy of preoperative stenting as a prophylaxis for EN. Several observational studies have shown promising effects of MPD stent in prevention of POPF but with limited evidence. In this study, we aim to include patients who are prone to suffer from POPF to validate the efficacy of MPD stent. In our previous research, we demonstrated the distance from insulinoma to MPD ≤2 mm was an independent risk factor for POPF. Therefore, it is a reasonable and feasible choice to confine patients whose tumors are “deep” in our ongoing trial. Preoperative MPD stent placement, as an extra intervention procedure for treating insulinoma, is still a vague yet practical technique in the prevention of POPF. Thus, the conduction of this clinical trial in a randomized controlled way is under the general ethical principle of clinical equipoise according to our present knowledge. In this way, the result of this multicenter, prospective, randomized control clinical trial can offer substantial information on the feasibility of this approach, and thus hopefully widen the indication of enucleation and partially alter the treatment pathway of insulinoma.

Author Contributions

Contributors GR, YB, CL, XQ, WW, ZY participated in creating the study design. GR drafted the manuscript. JJ, TX, ZY, WJ, CF, WZ, MZ, WM, GS provided a critical revision of the manuscript. XQ obtained the funding for this study. All the authors read and approved the final manuscript.

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Disclaimer The funder will have no role in the conduct or analysis of the trial.

Competing interests None declared.

Total word count: 2466

Figure 1 Flow chart of the study. FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; INS, insulin; C-pep, C-peptide; CE-CT, contrast-enhanced CT; US, ultrasound; DM, diabetes mellitus; ASA American Society of Anesthesiology.

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Box 1 Inclusion and exclusion criteria

Inclusion Criteria
➢ Age 18-75 years ➢ The clinical qualitative diagnosis of insulinoma was clear; ➢ The localization diagnosis was clear, and it was determined that the tumor was single, located in the head and neck; ➢ The distance between the tumor and the main pancreatic duct was determined to be ≤ 2mm by preoperative imaging (enhanced CT, MRI, etc.); ➢ Truly informed and voluntarily participate in this study, with written informed consent.
Exclusion Criteria
➢ Maximum diameter of the tumor >2cm proved pathologically ➢ Severe cardiopulmonary complications

- Combined with other known tumor diseases
- Invasive insulinoma or insulinoma with suspicious metastasis
- Previous upper abdominal surgery history
- Refusal or inability to cooperate in the study

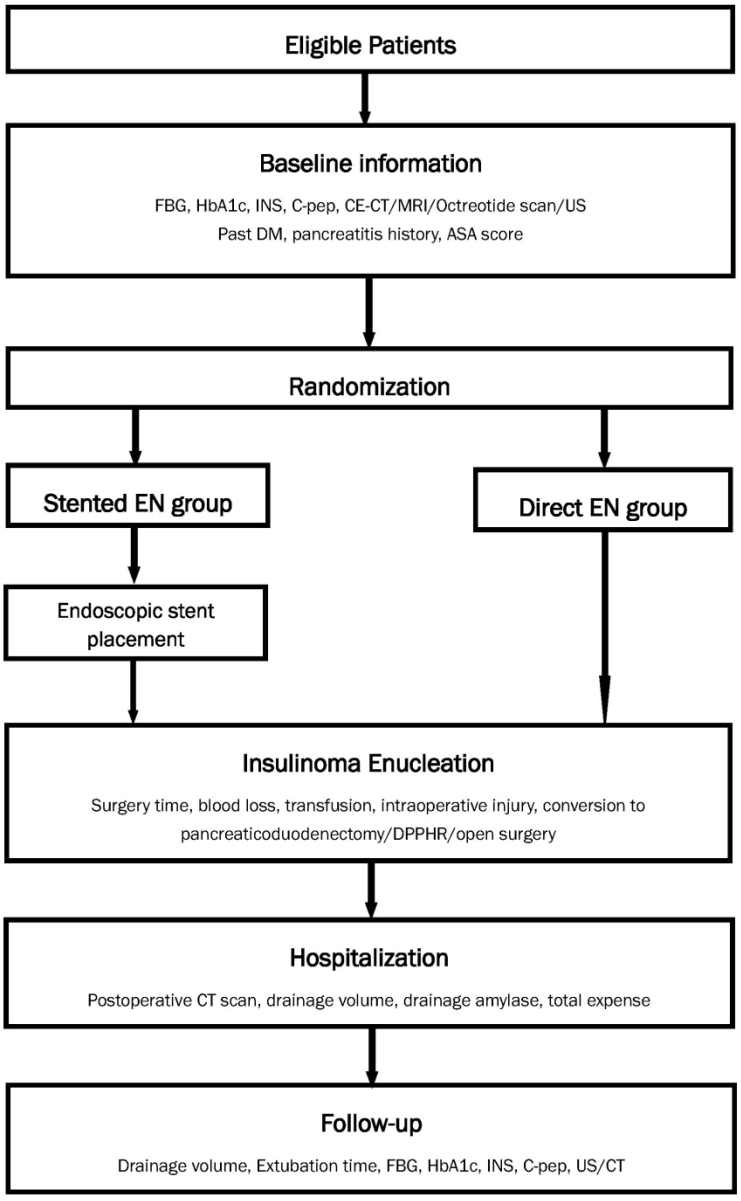

Figure 1 Flow chart of the study. FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; INS, insulin; C-pep, C-peptide; CE-CT, contrast-enhanced CT; US, ultrasound; DM, diabetes mellitus; ASA American Society of Anesthesiology.

147x232mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	1

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	7
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1&7
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if	7

		applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5-6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5-6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to	4

		conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4-5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	N/A

		collected for participants who discontinue or deviate from intervention protocols	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the	N/A

		protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from	3

		potential trial participants or authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	7
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See supplemental materials
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Study Protocol for Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct: a multicenter randomized Clinical Trial in Chinese Tertiary Medical Centers

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery, Diabetes and endocrinology
Keywords:	Pancreatic surgery < SURGERY, Pancreatic disease < GASTROENTEROLOGY, Endocrine tumours < ONCOLOGY

Study Protocol for Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct: a multicenter randomized Clinical Trial in Chinese Tertiary Medical Centers

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Abstract

Introduction
The surgical intervention approach to insulinomas in proximity to the main pancreatic duct remains controversial. Standard pancreatic resection is recommended by several guidelines; however, enucleation (EN) still attracts surgeons with less risk of late exocrine/endocrine insufficiency, despite a higher postoperative pancreatic fistula (POPF) rate. Recently, the efficacy and safety of preoperative pancreatic stents placement before the enucleation have been demonstrated. Thus, a multicenter open-label study is being conducted to evaluate the efficacy and safety of stents placement in improving the outcome of enucleation of insulinomas in proximity to the main pancreatic duct.

Methods and analysis
This is a prospective, randomized, open-label, superiority clinical trial conducted at multiple tertiary centers in China. The major eligibility criteria is the presence of insulinoma located in the head and neck of the pancreas in proximity(≤2mm) to the main pancreatic duct. Blocked randomization will be performed to allocate patients into the Stent EN group and the Direct EN group. Patients in the Stent EN group will go through stent placement by the endoscopist within 24 hours before the enucleation surgery, whereas other patients will receive enucleation surgery directly. The primary outcome is the assessment of the superiority of stent placement in reducing POPF rate measured by the International Study Group of Pancreatic Surgery (ISGPS) standard. Both interventions are performed in an inpatient setting and regular follow-up will be performed. The primary outcome (POPF rate) will be tested for superiority with the Chi-square test. The difference in secondary outcomes among the two groups will be analysed using appropriate tests.

Ethics and dissemination
The study was approved by the Peking Union Medical College Hospital Institutional Review Board (K23C0195). Results of the study will be published in an international peer-reviewed journal.

Trial registration number
ClinicalTrials. gov Registry (NCT05523778).

Keywords: Insulinoma, pancreatic duct stent, enucleation, postoperative pancreatic fistula

Article Summary

Strengths and limitations of this study

- A prospective multicenter clinical design to assess the efficacy and safety of a preventive intervention in improving the outcome of enucleation surgery.
- Recruiting patients from multiple tertiary medical centers across China.
- Local online communication tool exploited to promote interactions between investigators and patients

- The lack of blinding of the patients, surgeons, data collectors, and data analysts is the limitation of the study.

Introduction

Insulinomas are the most common functioning pancreatic neuroendocrine neoplasms, with an estimated incidence of 1–4 per million per year [1, 2] They are insulin-secreting tumors that cause common clinical features including neuroglycopenia and autonomic nervous system disorders caused by dysregulated secretion of insulin[3-5]. Surgical management remains the only curative modality for 90% of benign, localized insulinomas[4, 6].

According to several guidelines including the National Comprehensive Cancer Network (NCCN) and the European Neuroendocrine Tumor Society (ENETs)[7, 8], enucleation(EN), a parenchymal preserving modality, that could reduce the risk of late exocrine/endocrine insufficiency, should be considered as the first-line surgical approach for exophytic and peripheral insulinomas[9].

However, in cases of endophytic insulinomas or tumors in proximity to the main pancreatic duct (MPD), the optimal choice of surgical intervention is controversial. Standard pancreatic resection, such as pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), is indicated in guidelines while they aggressively eliminate normal pancreatic tissue, which can lead to long-term consequences including exocrine and endocrine pancreatic insufficiency [10, 11]. Recently, duodenum-preserving pancreatic head resection (DPPHR) was alternatively recommended for the resection of large PNETS.[12] In contrast, performing EN in cases with endophytic insulinomas and tumors in proximity to the MPD still baffles many surgeons as several retrospective researches suggested a significantly elevated rate of post-operative morbidity, especially postoperative pancreatic

fistula(POPF). Lu et.al compared post-operative morbidity between PD and EN, indicating a significant difference in POPF (18.1% vs 61.1%) between the two approaches[13], and Heeger K et al. reported the POPF rate as 70% (21 of 30 patients) after EN of pancreatic tumors located ≤ 3 mm from the MPD [14]. Another study involving 52 patients who underwent EN also demonstrated a high POPF rate of 60% in the group of tumors located at less than or equal to 2 mm from the MPD.[15]. Recently, Dokmak et.al suggested the proximity to MPD < 3 mm as an independent risk factor of POPF in enucleation[16]. Therefore, preventive measures in EN that decrease the POPF rate would encourage the implementation of EN thus improving the long-term benefits for patients with insulinomas in proximity to the MPD.

POPF is usually derived from intraoperative injuries to MPD. Prophylactic preoperative stenting is believed to prevent the MPD injury in that it not only helps to identify the location of MPD in the surgical field thus preventing intraoperative damage but also decompresses pancreatic duct by reducing pancreatic juice leakage from the resection plane and providing support to the duct when stricture develops. Pertinent clinical evidence involving stenting and EN is still lacking. Some researchers reported the usage of preoperative stenting as a prophylaxis for EN[17-21], and despite they all revealed the feasibility and safety of the technique, most of these researches involved a limited number of patients and were single-armed studies.

Based on the knowledge and shortcomings on this topic, our team has collected 18 patients undergoing preoperative stenting in our center for 5 years. We retrospectively analyzed the risk factor of postoperative complications, especially POPF, and discovered

that the distance from insulinoma to MPD ≤2 mm was an independent risk factor for POPF (OR =6.011, p = 0.003). In addition, the preoperative pancreatic stent substantially reduced the incidence of POPF in patients with tumors located in proximity to the MPD (37.5% vs 71.4%, p = 0.028) [22]. Therefore, we launched the current clinical trial to assess the efficacy and safety of preoperative stenting before EN of insulinoma in the head and neck of the pancreas in proximity to the MPD. According to the Evidence Map of Pancreatic Surgery (www.evidencemap.surgery), this is the first trial of its kind[23].

Methods and analysis

➢ Study setting

This is a multicenter, double-arm, prospective, randomized trial in five high-volume medical centers in China. Experienced surgeons will determine the eligibility of their patients and obtain informed consent forms. (see Supplementary Materials) Eligible patients with insulinoma in proximity to the MPD (≤2mm) will be allocated randomly into two groups: Stented EN group, where the pancreatic duct stents are placed in patients by endoscopist within 24 hours before the enucleation surgery, and Direct EN group, where patients receive direct enucleation surgery. An overview of the protocol is shown in Figure 1. The study started in February 2023 and was planned to finish patient recruitment in December 2025.

➢ Endpoints

Primary endpoint: Rate of POPF within 3 months after EN.

Secondary endpoints:

1) Rate of post-stent-placement acute pancreatitis in Stented EN group within in 3 weeks after EN

2) Operation time

3) Intraoperative blood loss

4) Rate of postoperative abdominal infection within 3 weeks after EN

5) Rate of postpancreatectomy hemorrhage(PPH) within 3 weeks after EN

6) Rate of postoperative lung infection within 3 weeks after EN

7) Rate of postoperative delayed gastric emptying within 3 weeks after EN

8) Rate of postoperative dyspepsia within 6 months after EN

9) Rate of postoperative hyperglycemia within 6 months after EN

10) Total cost of hospitalization

➢ Definition

In this study, POPF, delayed gastric emptying and PPH adopt the definition proposed by the international pancreatic surgery research group (ISGPS) [24-26]. Pancreatitis, abdominal infection, dyspepsia, lung infection, and hyperglycemia will be evaluated based on Common Terminology Criteria for Adverse Event (CTCAE) V.5.0. Severe adverse events are defined as grade 3 or higher in CTCAE.

➢ Patients eligibility

Inclusion and exclusion criteria are shown in Box 1

➢ Randomization

Randomization will be initiated by authorized investigators of the trial after checking the informed consent and the inclusion and exclusion criteria. Each eligible patient will be

allocated an individual code/randomization number, which has to be recorded in case report form (CRF). Blocked randomization (blocked number=4) for each center will be performed using SAS Studio by the study assistant prior to the beginning of enrollment. After randomization, surgeons in all centers who enroll the patient will be informed of the intervention assignment.

- Blindness

In accordance with recent academic recommendations on the implementation of blinding in surgical trials[27], meticulous consideration has been given to blinding strategies tailored to distinct study contributors, which encompass patients, surgeons, data collectors, data analysts, and outcome assessors. Patients participating in this study are deemed unblindable due to the number of patients with POPF was 6 (37.5%) and 20 (71.4%), respectively. According to the abovementioned POPF rate in two condition the intrinsic procedural difference between the two groups. Surgeons, who possess a direct line of sight to the presence of the stent during intraoperative procedures, are similarly unfeasible candidates for blinding. Data collectors also find themselves in a position where blinding is not viable, primarily due to the inevitable nature of their responsibilities, which involve the encounter of specific clinical data and records which are integral to prompt group allocation results. Examples of such records are operation records of stenting procedures and diagnostic CT imaging, which may conclusively reveal the presence of a stent within MPD. Furthermore, the integrity of data analysis relies on the unobstructed knowledge of group allocation results, rendering the blinding of data analysts unviable. Recognizing the critical importance of blinding in assessing primary and secondary endpoints, especially those

related to complications, outcome assessors are kept blinded to participant group allocation. Based on our protocol, the assessment of endpoints is directly linked with objective clinical data which can be provided to independent assessors with blindness of allocation. This strategy plays a pivotal role in reducing potential bias in the assessment of primary and secondary outcomes while concurrently insulating the operating surgeon from subjective judgment regarding clinical endpoints. Emergency unblinding is not deemed necessary.

➢ Study interventions

After baseline visit and admission, eligible participants are randomized to the stented EN group or the direct EN group, as shown in Figure 1.

■ Preoperative MPD stenting

The preoperative pancreatic duct stent was regarded as a possible effective method to prevent POPF. The single-pigtail pancreatic duct stent is usually placed within 24 hours before the enucleation endoscopically. The stent length should span the site of the tumor. The length and the diameter of the stent used should be recorded in CRF. The stent was removed by duodenoscopy about three months after surgery. Endoscopic stent placement and removal represents a common procedure at the Endoscopic Center of Peking Union Medical College Hospital and other centers and will be carried out by experienced endoscopists (minimum of 50 procedures) for the study. Any adverse events should be recorded in CRF including stent-related pancreatitis. Blood amylase is tested 2-4 hours after stenting before enucleation to discover potential stenting-related acute pancreatitis.

■ Enucleation

During the surgery, intraoperative ultrasound will be performed to evaluate the location of the tumor and the distance between the tumor and MPD. The peripheral pancreatic lobule covering the tumor will be exposed by the ultrasound scalpel. After exposure of the insulinoma, the surgeon sutures the lesion and suspends it, and then the insulinoma is dissected from the normal pancreatic tissue. Dissection was performed in contact with the lesion by a combination of harmonic scalpel and bipolar cautery. Frozen sections of resected specimens are regularly investigated to identify benign insulinomas. The operative field should be carefully examined and MPD disruption should be repaired immediately once detected. The prophylactic abdominal drainage tube is applied. Intraoperative conversion (to open procedure, DPPHR, or PD), surgery time, blood loss, and transfusion volume should be recorded in CRF.

- Postoperative management

General clinical treatment and PF prevention treatment will be conducted in both two groups. The patient's body temperature and drainage volume were recorded daily. The amount and the amylase concentration of the drainage fluid as well as the blood was routinely measured on the 1st, 3rd, 5th, and 7th postoperative days. Extubation would be considered if the drainage volume is less than 10 ml for 3 consecutive days or the amylase level of the drainage solution is less than three times the upper limit of normal. If the drainage tube has not been removed at the time of discharge, the patient would be instructed to record the daily drainage until extubation in the outpatient setting.

- Follow-up

For the first three months after discharge, patients should maintain a regular follow-up session for every two weeks through outpatient or telephone. The following information should be collected during each follow-up: basic information and general condition of the patient, whether the patient has been extubated (if not extubated, record the recent drainage condition), recent medical interventions, and possible manifestations of dyspepsia or hyperglycemia. Laboratory tests and imaging examinations will be done at the surgeon's discretion. Normally, CT or MRI scans will be performed routinely at 3 months postoperatively, just before stent removal, and then again 3 months after the stent removal.

- Statistical methods
  - Hypothesis
    - Null hypothesis

The rate of POPF in patients who undergo MPD stent placement before enucleation is not less than that of patients who undergo enucleation directly.

    - Alternative hypothesis

The rate of POPF in patients who undergo MPD stent placement before enucleation is less than that of patients who undergo enucleation directly.

  - Sample size calculation

In our previous retrospective study, a total of 44 patients with insulinoma in proximity to the MPD who underwent enucleation were included, of which 16 had stent placement and 28 had no stent placement, ands, 38 evaluable patients per group will provide 85% power to reject the null hypothesis in a Z test(unpooled) for superiority at a one-sided significance

level of 0.05 considering the POPF rate difference of at least 5% to represent a clinically relevant difference. Therefore, 78 patients in total are to be recruited in the study considering possible dropout.

- Statistical analysis

The primary outcome (rate of POPF) will be tested for superiority with a Chi-square test assuming a superiority difference of 5% with a one-sided significance level of 0.05. All patients undergoing EN will be included. The analysis will be performed twice: firstly after about 50% of the patients have been discharged and secondly after all patients have finished the follow-up procedure. Secondary outcomes will be described by calculating means or relative frequencies for each treatment group with 95% CIs. Differences in secondary outcomes between two groups will be analyzed using appropriate tests (Shapiro-Wilk tests, t-tests, Mann-Whitney U tests, Wilcoxon rank-sum tests, Chi-square tests, Fisher's exact tests, etc.).

Ethics and dissemination

Written informed consent from all the patients screened will be obtained before the procedures start. The study protocol has been approved by the Peking Union Medical College Hospital Institutional Review Board(approval number K23C0195) and registered in ClinicalTrials.gov(NCT05523778). The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki[28]. Throughout the study, all data acquired in this trial will be provided to the involved investigators and ethics committee members for monitoring, audits, and inspections. Results will be published in an international peer-reviewed journal.

In response to the submission and approval of our protocol, several modifications have been incorporated into the study design, all of which have undergone thorough scrutiny and received approval from our ethics committee. Firstly, a new timepoint at postoperative day 7 (pod7) has been added for the measurement of amylase levels, leveraging the existing practice of routinely measuring amylase levels for all patients at this timepoint. Secondly, we have introduced an exclusion criterion based on the maximum diameter of the tumor (>2cm), a feasible addition given that no enrolled patients before this change meet the exclusion criteria. Thirdly, a significant refinement involves blinding outcome assessors, a practicable adjustment as assessors can re-evaluate outcomes solely based on the information recorded in the case report form (CRF). Lastly, we have clarified that the primary outcome measurement will occur at 90 days postoperatively, enhancing precision in reporting the study's findings. These modifications aim to strengthen the study's scientific integrity, participant safety, and overall methodological rigor.

- Patient and public involvement

Throughout the study, a study account based on a local online communication tool (WeChat) will be established to receive any suggestions and consultations from patients involved and information about the study will be updated for all patients who subscribed to the study account.

Discussion

Generally, enucleation is preferred over other operation approaches in treating insulinomas, as it circumvents complicated reconstructions and possible subsequent complications.

However, POPF is common in the enucleation of insulinomas that are in proximal to MPD, which limits its clinical application. In this clinical trial, we aim to demonstrate the safety and efficacy of preoperative stenting as a prophylaxis for EN. Several observational studies have shown promising effects of MPD stent in prevention of POPF but with limited evidence. In this study, we aim to include patients who are prone to suffer from POPF to validate the efficacy of MPD stent. In our previous research, we demonstrated the distance from insulinoma to MPD ≤2 mm was an independent risk factor for POPF. Therefore, it is a reasonable and feasible choice to confine patients whose tumors are "deep" in our ongoing trial. Preoperative MPD stent placement, as an extra intervention procedure for treating insulinoma, is still a vague yet practical technique in the prevention of POPF. Thus, the conduction of this clinical trial in a randomized controlled way is under the general ethical principle of clinical equipoise according to our present knowledge. In this way, the result of this multicenter, prospective, randomized control clinical trial can offer substantial information on the feasibility of this approach, and thus hopefully widen the indication of enucleation and partially alter the treatment pathway of insulinoma.

Author Contributions

Contributors GR, YB, CL, XQ, WW, ZY participated in creating the study design. GR drafted the manuscript. JJ, TX, ZY, WJ, CF, WZ, MZ, WM, GS provided a critical revision of the manuscript. XQ obtained the funding for this study. All the authors read and approved the final manuscript.

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Disclaimer The funder will have no role in the conduct or analysis of the trial.

Competing interests None declared.

Total word count: 2654

Figure 1 Flow chart of the study. FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; INS, insulin; C-pep, C-peptide; CE-CT, contrast-enhanced CT; US, ultrasound; DM, diabetes mellitus; ASA American Society of Anesthesiology.

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Box 1 Inclusion and exclusion criteria

Inclusion Criteria
➢ Age 18-75 years ➢ The clinical qualitative diagnosis of insulinoma was clear; ➢ The localization diagnosis was clear, and it was determined that the tumor was single, located in the head and neck; ➢ The distance between the tumor and the main pancreatic duct was determined to be ≤ 2mm by preoperative imaging (enhanced CT, MRI, etc.); ➢ Truly informed and voluntarily participate in this study, with written informed consent.
Exclusion Criteria
➢ Maximum diameter of the tumor >2cm proved pathologically ➢ Severe cardiopulmonary complications ➢ Combined with other known tumor diseases ➢ Invasive insulinoma or insulinoma with suspicious metastasis ➢ Previous upper abdominal surgery history ➢ Refusal or inability to cooperate in the study

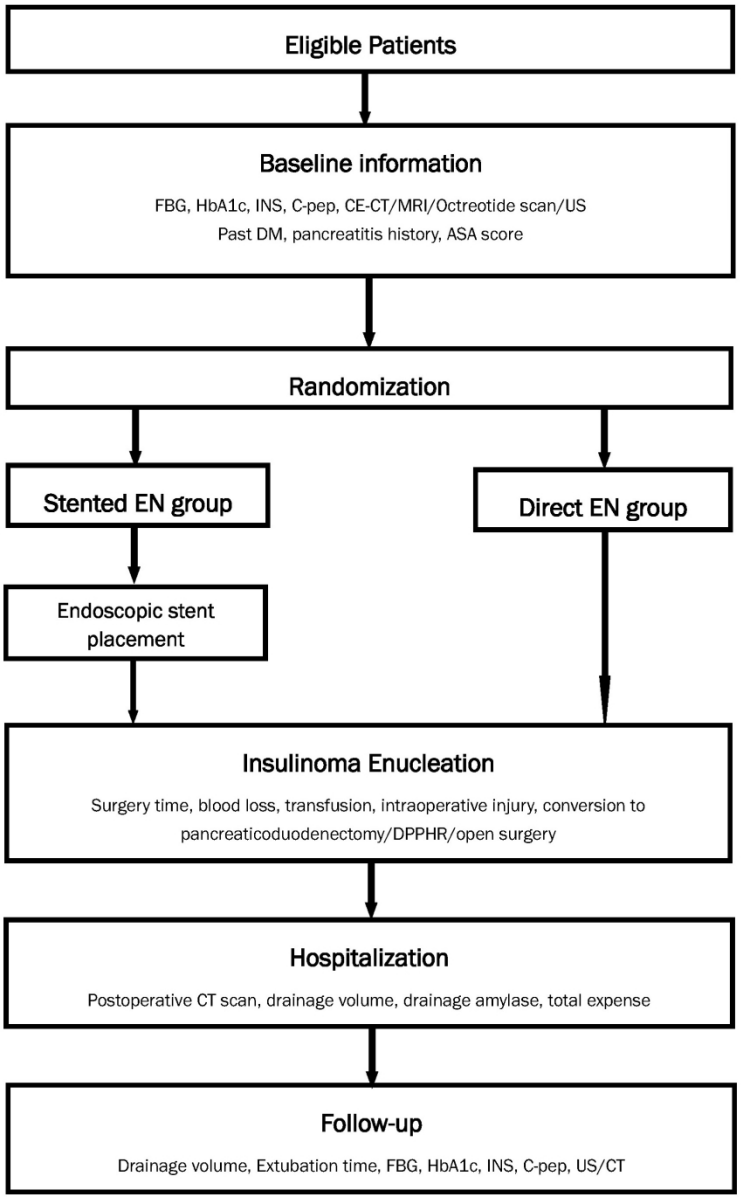

Figure 1 Flow chart of the study. FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; INS, insulin; C-pep, C-peptide; CE-CT, contrast-enhanced CT; US, ultrasound; DM, diabetes mellitus; ASA American Society of Anesthesiology.

147x232mm (300 x 300 DPI)

Written informed consent form

Medical Research Topics:	Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct
Protocol number (if applicable):	
Study Site:	Peking Union Medical College Hospital, Chinese Academy of Medical Sciences
Principal investigators:	Qiang Xu
Informed consent form Version No.	V3.0
Informed consent	2022/12/30

form version date _____

Subject Name: _____

Subject ID: _____

Dear Subject:

We would like to invite you to participate in a clinical study entitled "A Randomized Controlled Study of Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct ".

Before you decide whether to consent to participate, please read this informed consent form carefully and ask the investigators questions about your concerns. You may also ask your family, friends, or others. Once you have decided to participate in the study, you will be asked to sign this informed consent form.

1. Research Background

Insulinoma is the most common type of functional pancreatic endocrine tumors, which is characterized by uncontrolled excessive insulin secretion. Its main treatment is surgical resection. 90% of patients with insulinoma can be cured by surgical treatment. We found that for insulinomas located in the pancreatic head and neck near the main pancreatic duct, enucleation is prone to cause main pancreatic duct injury, which increases the risk of postoperative pancreatic fistula and other serious complications. Therefore, pancreaticoduodenectomy is recommended, but it requires combined resection of part of the stomach, duodenum, common bile duct and gallbladder, and there is a high risk of postoperative pancreatic exocrine insufficiency. In contrast, enucleation still has the advantages of less trauma and low incidence of long-term postoperative pancreatic secretion insufficiency, which is of great help to improve the long-term quality of life of patients after surgery. At present, the surgical management of this type of tumor is still inconclusive in the world, and many large pancreatic centers are still conducting clinical studies on enucleation. Studies have shown that preoperative placement of pancreatic duct stents followed by enucleation can reduce the incidence of postoperative pancreatic fistula and increase the long-term postoperative benefits, but the placement of pancreatic duct stents may cause stent-related adverse events. However, the placement of pancreatic stent may cause stent-related adverse events. However, there is no high-level clinical study to demonstrate its advantages and disadvantages. Therefore, the aim of this study is to investigate the safety and efficacy of preoperative pancreatic stent placement in patients with insulinoma in the pancreatic head and neck near the main pancreatic duct through a multi-center randomized controlled trial, so as to provide evidence-based medical evidence for standardized treatment of insulinoma and thus to change the current treatment guidelines.

This study was approved by the Peking Union Medical College Hospital Ethics Committee.

2. What was the purpose of this clinical study?

To compare the clinical efficacy, safety and efficacy between direct enucleation and preoperative placement of pancreatic stent followed by enucleation for insulinoma near the main pancreatic duct in the head and neck of the pancreas, and to evaluate the application value of the former surgical treatment strategy.

3. Methods: Study

This study was an intervention study. Participants were divided into two groups: experimental

group and control group. Enrollment in the two groups is 1:1, grouping will be random (like a lottery), and neither you nor the investigator can choose in advance which group to participate in. The study was unblinded, meaning that after randomization, you, the investigator, and the clinician knew which group you had been assigned to. The study had an anticipated enrollment of 78 patients nationwide.

4. Study PROCESS

Before commencing any research related activities, you will first need to sign this informed consent form.

During the screening period, the researcher will ask and collect your personal information, previous diagnosis and treatment, your combined medications, comorbidities, and order your blood routine, liver function, renal function, pancreatic function, fasting blood glucose, insulin, C-peptide, abdominal and pelvic enhanced CT, MRI and other examinations. We will determine whether you meet the inclusion criteria through your current clinical symptoms, performance, and examination results.

If you meet the eligibility criteria, study treatment will be initiated, and you will be randomly assigned to either an experimental group (placement of a pancreatic duct stent before enucleation) or a control group (enucleation alone). You will then proceed to endoscopic stent placement and surgery according to standard protocols.

During your hospitalization, we will collect your laboratory test results, surgery-related information, and recovery, which do not require your additional cooperation. If you are assigned to the experimental group, you will be scheduled to undergo ERCP-guided pancreatic duct stenting approximately 1 day before the procedure, which is in accordance with the usual practice of our hospital.

After you are discharged from the hospital, you are required to follow the doctor's advice for regular outpatient follow-up. At follow-up visits, the investigator will ask about your diet and measure your blood sugar. You will be contacted by telephone every 1 month to inquire about your postoperative recovery, diet, etc.

5. How the Study Ended

If you complete all study visits, the study will last for 24 months, and you will be scheduled for additional visits as needed during the study, after which you will be available at your usual frequency.

The study will conclude after the completion of the last subject's treatment, and it is anticipated that your time in the study may last 1-2 years.

You may opt out of the study at any time during the study, and the study physician may ask you to do so for your health and benefit. Prior to withdrawal, the study physician may order tests to ensure that you can exit safely. Your data will not be included in the results of the study, and your medical treatment and rights will not be affected.

During the course of the study, study physicians, study funders, regulatory authorities, and ethics committees may terminate the study.

6. Study Benefits

Your surgical outcome and long-term quality of life may improve by participating in this study, but we cannot guarantee that you will. You will receive careful evaluation, monitoring, and treatment beyond routine monitoring.

Your participation in this study may help physicians learn more about the effects of treatment for high-risk insulinomas, information that other patients with the same or similar conditions may benefit from in the future.

7. Research Risks and inconveniences

There are known or unknown risks associated with any research. Some are mild and transient, some are severe and permanent, and whether and which risks arise and their severity will vary from person to person. Your research physician will take all precautions and monitor your condition closely. If you experience any discomfort, be sure to inform your study physician immediately so that necessary treatment can be taken promptly.

Risks of study-related procedures: Preoperative ERCP endoscopy and pancreatic duct stenting may pose risks of pancreatitis, perforation, bleeding, and stent migration. There are risks of pancreatic fistula, bleeding, and infection after surgery, and these risks are also risks in the process of disease treatment. Participation in this study does not increase the incidence of these risks.

Possible inconvenience of the study: To participate in this study, you need to strictly record the amount of drainage and the time of extubation. The rest were the same as routine. Patients were followed up 4 times on time after the operation and completed the examinations required by the experiment (the number and content of follow-up visits were the same as the recommended routine diagnosis and treatment process for postoperative patients). Please take these inconvenients into account when deciding whether to participate in this study.

8. Alternatives that can be adopted

If you do not participate in the study, you can choose to perform pancreaticoduodenectomy or enucleation with or without pancreatic stent placement, as is standard practice for insulinoma management at this hospital. Your study physician will explain to you the potential benefits and risks of treatment.

9. New information during the study

During the course of the study, the investigator has acquired important and up-to-date information relevant to the study. We will keep you informed and it is up to you to decide whether to continue participating in the study.

10. Study-related costs

If you are assigned to the experimental group, you may be responsible for some study-related costs, which primarily include the cost of endoscopic procedures (including pancreatic stent

placement) that may be involved in the study. Regardless of whether you are assigned to the control group or the experimental group, medications and other routine tests are necessary in the course of routine clinical care and therefore will be paid for by you (or covered by medical insurance, if applicable). You will also have to pay for the treatment and tests you need for any coexisting medical conditions.

You will not be paid for your participation in the study, but the study will purchase clinical trial liability insurance for each patient who participates, which will be paid directly by the study investigators.

11. Study-related damages

If you experience any discomfort during the study, please contact the study doctor in time. The study doctor will guide you in the follow-up treatment. The researcher has purchased insurance for this study, and the insurance company will be responsible for the cost of treatment and reimbursement if you suffer any damage to your health as a result of participating in this study.

12. Confidentiality Policy

Your personal and medical information may be collected or processed in this study, including but not limited to: your name, gender, date of birth, address, telephone, diagnosis and treatment, examination, medical imaging, surgical records, etc.

Your personal information will be used only for the purposes described in the study protocol and this informed consent form.

Your medical information obtained by participating in this study will be kept confidential. The results of the study will also be published in academic journals without revealing any personally identifiable information about you.

13. Possible conflicts of interest from funding sources

This study was funded by the National High Level Hospital Clinical Research Funding of Peking Union Medical College Hospital, and there was no conflict of interest between the investigators and this study.

14. Voluntary Participation

Your participation is entirely voluntary. You may not participate or withdraw from the study at any time during the course of the study. This will not affect your relationship with the medical staff and your usual medical care will not be affected in any way.

15. Notes for Subjects

- Please tell the research doctor about your health status (especially whether you have other tumors and heart and lung diseases) and previous surgery history;
- Please follow the doctor's advice to the hospital on time for follow-up;
- If you feel any discomfort, please inform your research doctor in time;

16. Contact information

If you experience any discomfort, or if you have any questions about the study, you can contact the investigator at:

Position: Research physician	Name: Xu Qiang	Telephone number: 13810096103

If you have any questions about your rights as a subject, you can contact the Ethics Committee at:

Position: Ethics Secretary	Name: Li Jiayue	Phone number: 010-69156874

Thank you for reading and considering participation in the study.

17. Signature page

Subject:

I confirm the following information:

（1）I have read and understood the informed information and have had sufficient time to consider participation in the study.

（2）All my questions have been satisfactorily answered.

（3）I voluntarily participated in the study and followed the study procedures.

（4）I understand that I can withdraw from the study at any time without giving a reason and that my treatment or rights will not be affected.

（5）I have received an informed consent form and signed consent form for my retention.

（6）I agree to have my sample collected and used as described in this informed consent.

（7）I give permission for my personal information to be collected and used in this study.

（8）I understand that I may be contacted in the future to obtain my permission for this study or any related substudy.

By signing this document, I agree to participate in the study as stated in the Informed Information and consent form.

Subject's name (in block letters) :

Signature of Subject: Date:

The following is limited to the subject who is incapacitated, and the signature of the guardian is required.

[Subject's name (in block letters), relationship between guardian and subject is.]

Guardian's name (in block letters) : Contact Number:

Signature of Guardian: Date:

The following is limited to subjects without the ability to read and write, and the signature of an impartial witness is required.

Witness's name (in block letters) : Contact Number:

Signature of Witness: Date:

Name of investigator/authorizer (in block letters) :

Signature of investigator/authorizer: Date:

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	1

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	7
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1&7
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if	7

		applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5-6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5-6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to	4

		conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4-5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	N/A

		collected for participants who discontinue or deviate from intervention protocols	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the	N/A

		protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from	3

		potential trial participants or authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	7
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See supplemental materials
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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Study Protocol for Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct: a multicenter randomized Clinical Trial in Chinese Tertiary Medical Centers

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Study Protocol for Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct: a multicenter randomized Clinical Trial in Chinese Tertiary Medical Centers

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Abstract

Introduction

The surgical intervention approach to insulinomas in proximity to the main pancreatic duct remains controversial. Standard pancreatic resection is recommended by several guidelines; however, enucleation (EN) still attracts surgeons with less risk of late exocrine/endocrine insufficiency, despite a higher postoperative pancreatic fistula (POPF) rate. Recently, the efficacy and safety of preoperative pancreatic stents placement before the enucleation have been demonstrated. Thus, a multicenter open-label study is being conducted to evaluate the efficacy and safety of stents placement in improving the outcome of enucleation of insulinomas in proximity to the main pancreatic duct.

Methods and analysis

This is a prospective, randomized, open-label, superiority clinical trial conducted at multiple tertiary centers in China. The major eligibility criteria is the presence of insulinoma located in the head and neck of the pancreas in proximity(≤2mm) to the main pancreatic duct. Blocked randomization will be performed to allocate patients into the Stent EN group and the Direct EN group. Patients in the Stent EN group will go through stent placement by the endoscopist within 24 hours before the enucleation surgery, whereas other patients will receive enucleation surgery directly. The primary outcome is the assessment of the superiority of stent placement in reducing POPF rate

measured by the International Study Group of Pancreatic Surgery (ISGPS) standard. Both interventions will be performed in an inpatient setting and regular follow-up will be performed. The primary outcome (POPF rate) will be tested for superiority with the Chi-square test. The difference in secondary outcomes between the two groups will be analyzed using appropriate tests.

Ethics and dissemination

The study ha been approved by the Peking Union Medical College Hospital Institutional Review Board (K23C0195), Ruijin Hospital Ethics Committee (2023-314), Peking University First Hospital Ethics Committee (2024033-001), Institutional Review Board of Xuanwu Hospital of Capital Medical University (2023223-002), Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2023LSK-473), Institutional Review Board of Tongji Medical College Tongji Hospital (TJ-IRB202402059), Ethics Committee of Tongji Medical College Union Hospital (2023-0929), and Shanghai Cancer Center Institutional Review Board (2309282-16). The results of the study will be published in an international peer-reviewed journal.

Trial registration number

ClinicalTrials. gov Registry (NCT05523778).

Keywords: Insulinoma, pancreatic duct stent, enucleation, postoperative pancreatic fistula

Article Summary

Strengths and limitations of this study

- A prospective multicenter clinical design to assess the efficacy and safety of a

preventive intervention in improving the outcome of enucleation surgery.

- Recruiting patients from multiple tertiary medical centers across China.
- Local online communication tool exploited to promote interactions between investigators and patients
- The lack of blinding of the patients, surgeons, data collectors, and data analysts is the limitation of the study.

Introduction

Insulinomas are the most common functioning pancreatic neuroendocrine neoplasms, with an estimated incidence of 1–4 per million per year [1, 2] They are insulin-secreting tumors that cause common clinical features including neuroglycopenia and autonomic nervous system disorders caused by dysregulated secretion of insulin[3-5]. Surgical management remains the only curative modality for 90% of benign, localized insulinomas[4, 6].

According to several guidelines including the National Comprehensive Cancer Network (NCCN) and the European Neuroendocrine Tumor Society (ENETs)[7, 8], enucleation(EN), a parenchymal preserving modality, that could reduce the risk of late exocrine/endocrine insufficiency, should be considered as the first-line surgical approach for exophytic and peripheral insulinomas[9].

However, in cases of endophytic insulinomas or tumors in proximity to the main pancreatic duct (MPD), the optimal choice of surgical intervention is controversial. Standard pancreatic resection, such as pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), is indicated in guidelines while they aggressively eliminate normal pancreatic tissue, which can lead to long-term consequences including exocrine and endocrine pancreatic

insufficiency [10, 11]. Recently, duodenum-preserving pancreatic head resection (DPPHR) was alternatively recommended for the resection of large PNETS.[12] In contrast, performing EN in cases with endophytic insulinomas and tumors in proximity to the MPD still baffles many surgeons as several retrospective researches suggested a significantly elevated rate of postoperative morbidity, especially postoperative pancreatic fistula(POPF). Lu et.al compared postoperative morbidity between PD and EN, indicating a significant difference in POPF (18.1% vs 61.1%) between the two approaches[13], and Heeger K et al. reported the POPF rate as 70% (21 of 30 patients) after EN of pancreatic tumors located ≤3 mm from the MPD [14]. Another study involving 52 patients who underwent EN also demonstrated a high POPF rate of 60% in the group of tumors located at less than or equal to 2 mm from the MPD.[15]. Recently, Dokmak et.al suggested the proximity to MPD < 3 mm as an independent risk factor of POPF in enucleation[16]. Therefore, preventive measures in EN that decrease the POPF rate would encourage the implementation of EN thus improving the long-term benefits for patients with insulinomas in proximity to the MPD. POPF is usually derived from intraoperative injuries to MPD. Prophylactic preoperative stenting is believed to prevent the MPD injury in that it not only helps to identify the location of MPD in the surgical field thus preventing intraoperative damage but also decompresses pancreatic duct by reducing pancreatic juice leakage from the resection plane and providing support to the duct when stricture develops. Pertinent clinical evidence involving stenting and EN is still lacking. Some researchers reported the usage of preoperative stenting as a prophylaxis for EN[17-21], and despite they all revealed the feasibility and safety of the technique, most of these researches involved a limited number of patients

and were single-armed studies.

Based on the knowledge and shortcomings on this topic, our team has collected 18 patients undergoing preoperative stenting in our center for 5 years. We retrospectively analyzed the risk factor of postoperative complications, especially POPF, and discovered that the distance from insulinoma to MPD ≤2 mm was an independent risk factor for POPF (OR =6.011, p = 0.003). In addition, the preoperative pancreatic stent substantially reduced the incidence of POPF in patients with tumors located in proximity to the MPD (37.5% vs 71.4%, p = 0.028) [22]. Therefore, we launched the current clinical trial to assess the efficacy and safety of preoperative stenting before EN of insulinoma in the head and neck of the pancreas in proximity to the MPD. According to the Evidence Map of Pancreatic Surgery (www.evidencemap.surgery), this is the first trial of its kind[23].

Methods and analysis

- Study setting

This is a multicenter, double-arm, prospective, randomized trial in eight high-volume medical centers in China. Experienced surgeons will determine the eligibility of their patients and obtain informed consent forms. (see Supplementary Materials) Eligible patients with insulinoma in proximity to the MPD (≤2mm) will be allocated randomly into two groups: Stented EN group, where the pancreatic duct stents will be placed in patients by endoscopist within 24 hours before the enucleation surgery, and Direct EN group, where patients will receive direct enucleation surgery. An overview of the protocol is shown in Figure 1. The study started in February 2023 and is planned to finish patient recruitment in December 2025.

➢ Endpoints

Primary endpoint: Rate of POPF within 3 months after EN.

Secondary endpoints:

1) Rate of post-stent-placement acute pancreatitis in Stented EN group within in 3 weeks after EN
2) Operation time
3) Intraoperative blood loss
4) Rate of postoperative abdominal infection within 3 weeks after EN
5) Rate of postpancreatectomy hemorrhage(PPH) within 3 weeks after EN
6) Rate of postoperative lung infection within 3 weeks after EN
7) Rate of postoperative delayed gastric emptying within 3 weeks after EN
8) Rate of postoperative dyspepsia within 6 months after EN
9) Rate of postoperative hyperglycemia within 6 months after EN
10) Total cost of hospitalization

➢ Definition

In this study, POPF, delayed gastric emptying and PPH adopt the definition proposed by the International Pancreatic Surgery Research Group (ISGPS) [24-26]. Pancreatitis, abdominal infection, dyspepsia, lung infection, and hyperglycemia will be evaluated based on Common Terminology Criteria for Adverse Event (CTCAE) V.5.0. Severe adverse events are defined as grade 3 or higher in CTCAE.

➢ Patients eligibility

Inclusion and exclusion criteria are shown in Box 1

➢ Randomization

Randomization will be initiated by authorized investigators of the trial after checking the informed consent and the inclusion and exclusion criteria. Each eligible patient will be allocated an individual code/randomization number, which has to be recorded in case report form (CRF). Blocked randomization (blocked number=4) for each center will be performed using SAS Studio by the study assistant prior to the beginning of enrollment. After randomization, surgeons in all centers who enroll the patient will be informed of the intervention assignment.

➢ Blindness

Following recent academic recommendations on the implementation of blinding in surgical trials[27], meticulous consideration has been given to blinding strategies tailored to distinct study contributors, which encompass patients, surgeons, data collectors, data analysts, and outcome assessors. Patients participating in this study are deemed unblindable due to the intrinsic procedural difference between the two groups. Surgeons, who possess a direct line of sight to the presence of the stent during intraoperative procedures, are similarly unfeasible candidates for blinding. Data collectors also find themselves in a position where blinding is not viable, primarily due to the inevitable nature of their responsibilities, which involve the encounter of specific clinical data and records that are integral to prompt group allocation results. Examples of such records are operation records of stenting procedures and diagnostic CT imaging, which may conclusively reveal the presence of a stent within MPD. Furthermore, the integrity of data analysis relies on the unobstructed knowledge of group allocation results, rendering the blinding of data analysts

unviable. Recognizing the critical importance of blinding in assessing primary and secondary endpoints, especially those related to complications, outcome assessors are kept blinded to participant group allocation. Based on our protocol, the assessment of endpoints is directly linked with objective clinical data which can be provided to independent assessors with blindness of allocation. This strategy plays a pivotal role in reducing potential bias in the assessment of primary and secondary outcomes while concurrently insulating the operating surgeon from subjective judgment regarding clinical endpoints. Emergency unblinding is not deemed necessary.

- Study interventions

After baseline visit and admission, eligible participants will be randomized to the stented EN group or the direct EN group, as shown in Figure 1.

  - Preoperative MPD stenting

The preoperative pancreatic duct stent was regarded as a possible effective method to prevent POPF. The single-pigtail pancreatic duct stent is usually placed within 24 hours before the enucleation endoscopically. The stent length should span the site of the tumor. The length and the diameter of the stent used will be recorded in CRF. The stent will beremoved by duodenoscopy about three months after surgery. Endoscopic stent placement and removal represent a common procedure at the Endoscopic Center of Peking Union Medical College Hospital and other centers and will be carried out by experienced endoscopists (minimum of 50 procedures) for the study. Any adverse events will be recorded in CRF including stent-related pancreatitis. Blood amylase will be tested

2-4 hours after stenting before enucleation to discover potential stenting-related acute pancreatitis.

- Enucleation

During the surgery, intraoperative ultrasound will be performed to evaluate the location of the tumor and the distance between the tumor and MPD. The peripheral pancreatic lobule covering the tumor will be exposed by the ultrasound scalpel. After exposure of the insulinoma, the surgeon will suture the lesion and suspend it, and then the insulinoma will be dissected from the normal pancreatic tissue. Dissection will be performed in contact with the lesion by a combination of harmonic scalpel and bipolar cautery. Frozen sections of resected specimens will be regularly investigated to identify benign insulinomas. The operative field will be carefully examined and MPD disruption will be repaired immediately once detected. The prophylactic abdominal drainage tube will be applied. Intraoperative conversion (to open procedure, DPPHR, or PD), surgery time, blood loss, and transfusion volume will be recorded in CRF.

- Postoperative management

General clinical treatment and PF prevention treatment will be conducted in both two groups. The patient's body temperature and drainage volume were recorded daily. The amount and the amylase concentration of the drainage fluid as well as the blood will be routinely measured on the 1st, 3rd, 5th, and 7th postoperative days. Extubation would be considered if the drainage volume is less than 10 ml for 3 consecutive days or the amylase level of the drainage solution is less than three times the upper limit of normal. If the

drainage tube has not been removed at the time of discharge, the patient will be instructed to record the daily drainage until extubation in the outpatient setting.

- Follow-up

For the first three months after discharge, patients should maintain a regular follow-up session every two weeks through outpatient or telephone. The following information will be collected during each follow-up: basic information and the general condition of the patient, whether the patient has been extubated (if not extubated, record the recent drainage condition), recent medical interventions, and possible manifestations of dyspepsia or hyperglycemia. Laboratory tests and imaging examinations will be done at the surgeon's discretion. Normally, CT or MRI scans will be performed routinely at 3 months postoperatively, just before stent removal, and then again 3 months after the stent removal.

- Statistical methods

  - Hypothesis

    - Null hypothesis

    The rate of POPF in patients who undergo MPD stent placement before enucleation is not less than that of patients who undergo enucleation directly.

    - Alternative hypothesis

    The rate of POPF in patients who undergo MPD stent placement before enucleation is less than that of patients who undergo enucleation directly.

  - Sample size calculation

In our previous retrospective study, a total of 44 patients with insulinoma in proximity to the MPD who underwent enucleation were included, of which 16 had stent placement and 28

had no stent placement, and the number of patients with POPF was 6 (37.5%) and 20 (71.4%), respectively. According to the abovementioned POPF rate in two conditions, 38 evaluable patients per group will provide 85% power to reject the null hypothesis in a Z test (unpooled) for superiority at a one-sided significance level of 0.05 considering the POPF rate difference of at least 5% to represent a clinically relevant difference. Therefore, 78 patients in total are to be recruited in the study considering possible dropout.

- Statistical analysis

The primary outcome (rate of POPF) will be tested for superiority with a Chi-square test assuming a superiority difference of 5% with a one-sided significance level of 0.05. All patients undergoing EN will be included. The analysis will be performed twice: firstly after about 50% of the patients have been discharged and secondly after all patients have finished the follow-up procedure. Secondary outcomes will be described by calculating means or relative frequencies for each treatment group with 95% CIs. Differences in secondary outcomes between two groups will be analyzed using appropriate tests (Shapiro-Wilk tests, t-tests, Mann-Whitney U tests, Wilcoxon rank-sum tests, Chi-square tests, Fisher's exact tests, etc.).

Ethics and dissemination

Written informed consent from all the patients screened will be obtained before the procedures start. The study protocol has been approved by the Peking Union Medical College Hospital Institutional Review Board (approval number K23C0195), Ruijin Hospital Ethics Committee (2023-314), Peking University First Hospital Ethics Committee (2024033-001), Institutional Review Board of Xuanwu Hospital of Capital Medical

University (2023223-002), Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2023LSK-473), Institutional Review Board of Tongji Medical College Tongji Hospital (TJ-IRB202402059), Ethics Committee of Tongji Medical College Union Hospital (2023-0929), and Shanghai Cancer Center Institutional Review Board (2309282-16) and registered in ClinicalTrials.gov(NCT05523778). The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki[28]. Throughout the study, all data acquired in this trial will be provided to the involved investigators and ethics committee members for monitoring, audits, and inspections. Results will be published in an international peer-reviewed journal.

In response to the submission and approval of our protocol, several modifications have been incorporated into the study design, all of which have undergone thorough scrutiny and received approval from our ethics committee. Firstly, a new timepoint at postoperative day 7 (pod7) has been added for the measurement of amylase levels, leveraging the existing practice of routinely measuring amylase levels for all patients at this time point. Secondly, we have introduced an exclusion criterion based on the maximum diameter of the tumor (>2cm), a feasible addition given that no enrolled patients before this change met the exclusion criteria. Thirdly, a significant refinement involves blinding outcome assessors, a practicable adjustment as assessors can re-evaluate outcomes solely based on the information recorded in the case report form (CRF). Lastly, we have clarified that the primary outcome measurement will occur at 90 days postoperatively, enhancing precision in reporting the study's findings. These modifications aim to strengthen the study's scientific integrity, participant safety, and overall methodological rigor.

- Patient and public involvement

Throughout the study, a study account based on a local online communication tool (WeChat) will be established to receive any suggestions and consultations from patients involved and information about the study will be updated for all patients who subscribed to the study account.

Discussion

Generally, enucleation is preferred over other operation approaches in treating insulinomas, as it circumvents complicated reconstructions and possible subsequent complications. However, POPF is common in the enucleation of insulinomas that are in proximal to MPD, which limits its clinical application. In this clinical trial, we aim to demonstrate the safety and efficacy of preoperative stenting as a prophylaxis for EN. Several observational studies have shown promising effects of MPD stent in the prevention of POPF but with limited evidence. In this study, we aim to include patients who are prone to suffer from POPF to validate the efficacy of MPD stent. In our previous research, we demonstrated the distance from insulinoma to MPD ≤2 mm was an independent risk factor for POPF. Therefore, it is a reasonable and feasible choice to confine patients whose tumors are “deep” in our ongoing trial. Preoperative MPD stent placement, as an extra intervention procedure for treating insulinoma, is still a vague yet practical technique in the prevention of POPF. Thus, the conduction of this clinical trial in a randomized controlled way is under the general ethical principle of clinical equipoise according to our present knowledge. In this way, the result of this multicenter, prospective, randomized control clinical trial can offer substantial

information on the feasibility of this approach, and thus hopefully widen the indication of enucleation and partially alter the treatment pathway of insulinoma.

Author Contributions

Contributors GR, YB, CL, XQ, WW, ZY participated in creating the study design. GR drafted the manuscript. JJ, TX, ZY, WJ, CF, WZ, MZ, WM, GS provided a critical revision of the manuscript. XQ obtained the funding for this study. All the authors read and approved the final manuscript.

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Disclaimer The funder will have no role in the conduct or analysis of the trial.

Competing interests None declared.

Total word count: 2654

Figure 1 Flow chart of the study. FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; INS, insulin; C-pep, C-peptide; CE-CT, contrast-enhanced CT; US, ultrasound; DM, diabetes mellitus; ASA American Society of Anesthesiology.

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27. Probst, P., et al., *Evidence-based recommendations for blinding in surgical trials.*

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28. *Declaration of Helsinki*. October 2013:[Available from: http://www.wma.net/en/30publications/10policies/b3/index.html.

Box 1 Inclusion and exclusion criteria

Inclusion Criteria
➢ Age 18-75 years ➢ The clinical qualitative diagnosis of insulinoma is clear; ➢ The localization diagnosis is clear, and it was determined that the tumor is single, located in the head and neck; ➢ The distance between the tumor and the main pancreatic duct is determined to be ≤ 2mm by preoperative imaging (enhanced CT, MRI, etc.);

➢ Truly informed and voluntarily participate in this study, with written informed consent.
Exclusion Criteria
➢ Maximum diameter of the tumor >2cm proved pathologically ➢ Severe cardiopulmonary complications ➢ Combined with other known tumor diseases ➢ Invasive insulinoma or insulinoma with suspicious metastasis ➢ Previous upper abdominal surgery history ➢ Refusal or inability to cooperate in the study

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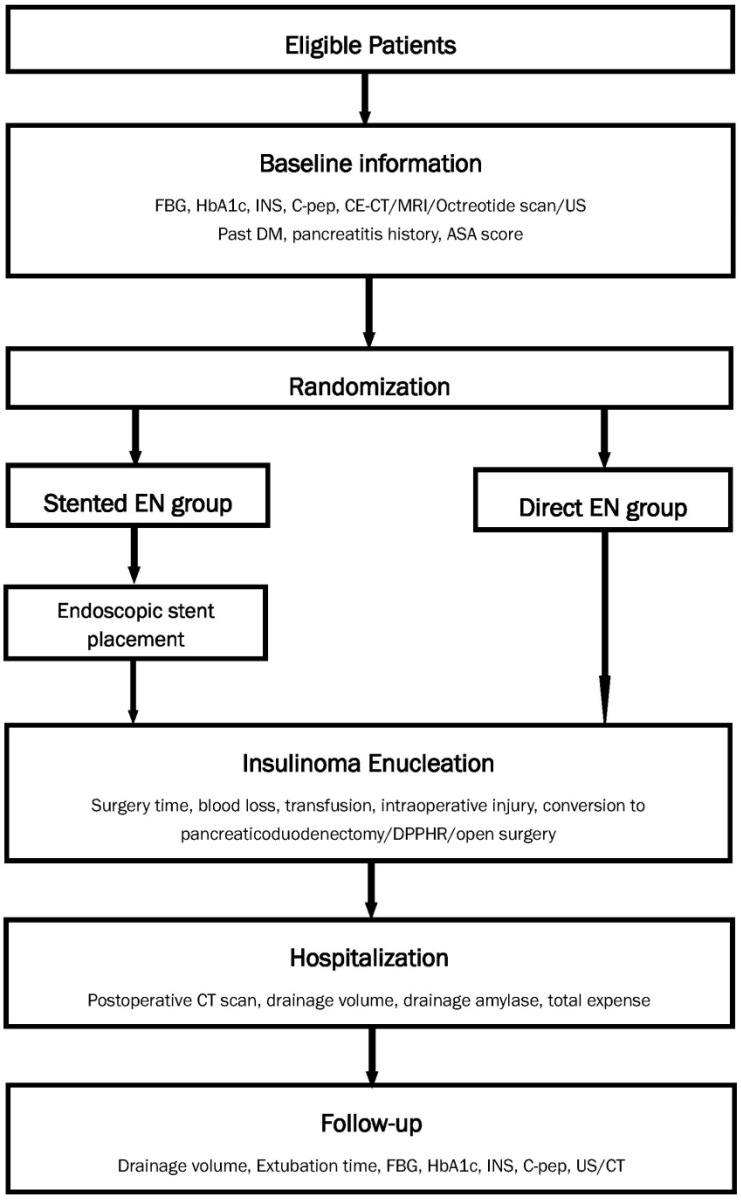

Figure 1 Flow chart of the study. FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; INS, insulin; C-pep, C-peptide; CE-CT, contrast-enhanced CT; US, ultrasound; DM, diabetes mellitus; ASA American Society of Anesthesiology.

147x232mm (300 x 300 DPI)

Written informed consent form

Medical Research Topics:	Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct
Protocol number (if applicable):	
Study Site:	Peking Union Medical College Hospital, Chinese Academy of Medical Sciences
Principal investigators:	Qiang Xu
Informed consent form Version No.	V3.0
Informed consent	2022/12/30

form version date

Subject Name:

Subject ID:

Dear Subject:

We would like to invite you to participate in a clinical study entitled "A Randomized Controlled Study of Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct ".

Before you decide whether to consent to participate, please read this informed consent form carefully and ask the investigators questions about your concerns. You may also ask your family, friends, or others. Once you have decided to participate in the study, you will be asked to sign this informed consent form.

1. Research Background

Insulinoma is the most common type of functional pancreatic endocrine tumors, which is characterized by uncontrolled excessive insulin secretion. Its main treatment is surgical resection. 90% of patients with insulinoma can be cured by surgical treatment. We found that for insulinomas located in the pancreatic head and neck near the main pancreatic duct, enucleation is prone to cause main pancreatic duct injury, which increases the risk of postoperative pancreatic fistula and other serious complications. Therefore, pancreaticoduodenectomy is recommended, but it requires combined resection of part of the stomach, duodenum, common bile duct and gallbladder, and there is a high risk of postoperative pancreatic exocrine insufficiency. In contrast, enucleation still has the advantages of less trauma and low incidence of long-term postoperative pancreatic secretion insufficiency, which is of great help to improve the long-term quality of life of patients after surgery. At present, the surgical management of this type of tumor is still inconclusive in the world, and many large pancreatic centers are still conducting clinical studies on enucleation. Studies have shown that preoperative placement of pancreatic duct stents followed by enucleation can reduce the incidence of postoperative pancreatic fistula and increase the long-term postoperative benefits, but the placement of pancreatic duct stents may cause stent-related adverse events. However, the placement of pancreatic stent may cause stent-related adverse events. However, there is no high-level clinical study to demonstrate its advantages and disadvantages. Therefore, the aim of this study is to investigate the safety and efficacy of preoperative pancreatic stent placement in patients with insulinoma in the pancreatic head and neck near the main pancreatic duct through a multi-center randomized controlled trial, so as to provide evidence-based medical evidence for standardized treatment of insulinoma and thus to change the current treatment guidelines.

This study was approved by the Peking Union Medical College Hospital Ethics Committee.

2. What was the purpose of this clinical study?

To compare the clinical efficacy, safety and efficacy between direct enucleation and preoperative placement of pancreatic stent followed by enucleation for insulinoma near the main pancreatic duct in the head and neck of the pancreas, and to evaluate the application value of the former surgical treatment strategy.

3. Methods: Study

This study was an intervention study. Participants were divided into two groups: experimental

group and control group. Enrollment in the two groups is 1:1, grouping will be random (like a lottery), and neither you nor the investigator can choose in advance which group to participate in. The study was unblinded, meaning that after randomization, you, the investigator, and the clinician knew which group you had been assigned to. The study had an anticipated enrollment of 78 patients nationwide.

4. Study PROCESS

Before commencing any research related activities, you will first need to sign this informed consent form.

During the screening period, the researcher will ask and collect your personal information, previous diagnosis and treatment, your combined medications, comorbidities, and order your blood routine, liver function, renal function, pancreatic function, fasting blood glucose, insulin, C-peptide, abdominal and pelvic enhanced CT, MRI and other examinations. We will determine whether you meet the inclusion criteria through your current clinical symptoms, performance, and examination results.

If you meet the eligibility criteria, study treatment will be initiated, and you will be randomly assigned to either an experimental group (placement of a pancreatic duct stent before enucleation) or a control group (enucleation alone). You will then proceed to endoscopic stent placement and surgery according to standard protocols.

During your hospitalization, we will collect your laboratory test results, surgery-related information, and recovery, which do not require your additional cooperation. If you are assigned to the experimental group, you will be scheduled to undergo ERCP-guided pancreatic duct stenting approximately 1 day before the procedure, which is in accordance with the usual practice of our hospital.

After you are discharged from the hospital, you are required to follow the doctor's advice for regular outpatient follow-up. At follow-up visits, the investigator will ask about your diet and measure your blood sugar. You will be contacted by telephone every 1 month to inquire about your postoperative recovery, diet, etc.

5. How the Study Ended

If you complete all study visits, the study will last for 24 months, and you will be scheduled for additional visits as needed during the study, after which you will be available at your usual frequency.

The study will conclude after the completion of the last subject's treatment, and it is anticipated that your time in the study may last 1-2 years.

You may opt out of the study at any time during the study, and the study physician may ask you to do so for your health and benefit. Prior to withdrawal, the study physician may order tests to ensure that you can exit safely. Your data will not be included in the results of the study, and your medical treatment and rights will not be affected.

During the course of the study, study physicians, study funders, regulatory authorities, and ethics committees may terminate the study.

6. Study Benefits

Your surgical outcome and long-term quality of life may improve by participating in this study, but we cannot guarantee that you will. You will receive careful evaluation, monitoring, and treatment beyond routine monitoring.

Your participation in this study may help physicians learn more about the effects of treatment for high-risk insulinomas, information that other patients with the same or similar conditions may benefit from in the future.

7. Research Risks and inconveniences

There are known or unknown risks associated with any research. Some are mild and transient, some are severe and permanent, and whether and which risks arise and their severity will vary from person to person. Your research physician will take all precautions and monitor your condition closely. If you experience any discomfort, be sure to inform your study physician immediately so that necessary treatment can be taken promptly.

Risks of study-related procedures: Preoperative ERCP endoscopy and pancreatic duct stenting may pose risks of pancreatitis, perforation, bleeding, and stent migration. There are risks of pancreatic fistula, bleeding, and infection after surgery, and these risks are also risks in the process of disease treatment. Participation in this study does not increase the incidence of these risks.

Possible inconvenience of the study: To participate in this study, you need to strictly record the amount of drainage and the time of extubation. The rest were the same as routine. Patients were followed up 4 times on time after the operation and completed the examinations required by the experiment (the number and content of follow-up visits were the same as the recommended routine diagnosis and treatment process for postoperative patients). Please take these inconvenients into account when deciding whether to participate in this study.

8. Alternatives that can be adopted

If you do not participate in the study, you can choose to perform pancreaticoduodenectomy or enucleation with or without pancreatic stent placement, as is standard practice for insulinoma management at this hospital. Your study physician will explain to you the potential benefits and risks of treatment.

9. New information during the study

During the course of the study, the investigator has acquired important and up-to-date information relevant to the study. We will keep you informed and it is up to you to decide whether to continue participating in the study.

10. Study-related costs

If you are assigned to the experimental group, you may be responsible for some study-related costs, which primarily include the cost of endoscopic procedures (including pancreatic stent

placement) that may be involved in the study. Regardless of whether you are assigned to the control group or the experimental group, medications and other routine tests are necessary in the course of routine clinical care and therefore will be paid for by you (or covered by medical insurance, if applicable). You will also have to pay for the treatment and tests you need for any coexisting medical conditions.

You will not be paid for your participation in the study, but the study will purchase clinical trial liability insurance for each patient who participates, which will be paid directly by the study investigators.

11. Study-related damages

If you experience any discomfort during the study, please contact the study doctor in time. The study doctor will guide you in the follow-up treatment. The researcher has purchased insurance for this study, and the insurance company will be responsible for the cost of treatment and reimbursement if you suffer any damage to your health as a result of participating in this study.

12. Confidentiality Policy

Your personal and medical information may be collected or processed in this study, including but not limited to: your name, gender, date of birth, address, telephone, diagnosis and treatment, examination, medical imaging, surgical records, etc.

Your personal information will be used only for the purposes described in the study protocol and this informed consent form.

Your medical information obtained by participating in this study will be kept confidential. The results of the study will also be published in academic journals without revealing any personally identifiable information about you.

13. Possible conflicts of interest from funding sources

This study was funded by the National High Level Hospital Clinical Research Funding of Peking Union Medical College Hospital, and there was no conflict of interest between the investigators and this study.

14. Voluntary Participation

Your participation is entirely voluntary. You may not participate or withdraw from the study at any time during the course of the study. This will not affect your relationship with the medical staff and your usual medical care will not be affected in any way.

15. Notes for Subjects

- Please tell the research doctor about your health status (especially whether you have other tumors and heart and lung diseases) and previous surgery history;
- Please follow the doctor's advice to the hospital on time for follow-up;
- If you feel any discomfort, please inform your research doctor in time;

16. Contact information

If you experience any discomfort, or if you have any questions about the study, you can contact the investigator at:

Position: Research physician	Name: Xu Qiang	Telephone number: 13810096103

If you have any questions about your rights as a subject, you can contact the Ethics Committee at:

Position: Ethics Secretary	Name: Li Jiayue	Phone number: 010-69156874

Thank you for reading and considering participation in the study.

17. Signature page

Subject:

I confirm the following information:

（1）I have read and understood the informed information and have had sufficient time to consider participation in the study.

（2）All my questions have been satisfactorily answered.

（3）I voluntarily participated in the study and followed the study procedures.

（4）I understand that I can withdraw from the study at any time without giving a reason and that my treatment or rights will not be affected.

（5）I have received an informed consent form and signed consent form for my retention.

（6）I agree to have my sample collected and used as described in this informed consent.

（7）I give permission for my personal information to be collected and used in this study.

（8）I understand that I may be contacted in the future to obtain my permission for this study or any related substudy.

By signing this document, I agree to participate in the study as stated in the Informed Information and consent form.

Subject's name (in block letters) :

Signature of Subject: Date:

The following is limited to the subject who is incapacitated, and the signature of the guardian is required.

[Subject's name (in block letters), relationship between guardian and subject is.]

Guardian's name (in block letters) : Contact Number:

Signature of Guardian: Date:

The following is limited to subjects without the ability to read and write, and the signature of an impartial witness is required.

Witness's name (in block letters) : Contact Number:

Signature of Witness: Date:

Name of investigator/authorizer (in block letters) :

Signature of investigator/authorizer: Date:

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	1

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	7
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1&7
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	7
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if	7

		applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5-6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5-6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to	4

		conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4-5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	N/A

		collected for participants who discontinue or deviate from intervention protocols	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the	N/A

		protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from	3

		potential trial participants or authorised surrogates, and how (see Item 32)	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	7

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	7
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	7
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See supplemental materials
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A