Ligation of pancreatic stump with quantified force during distal pancreatectomy for postoperative pancreatic fistula: study protocol for a single center non-randomized controlled clinical study.

Lufeng Chang, Jiongxin Xiong, Ming Yang, Yuxin Yang, Tao Peng, Tao Yin, Heshui Wu, Shanmiao Gou

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Abstract

Background: The closure of pancreatic stump after distal pancreatectomy remains controversial. Currently, the main methods of pancreatic stump closure include manual suturing and stapler closure. However, both methods carry a high risk of postoperative pancreatic fistula, which may be associated with the difficulty of balancing the provision of sufficient pancreatic duct burst pressure and ensuring blood supply to the stump.

Objective: This study aims to investigate whether the ligation of the pancreatic stump with quantified force can decrease the risk of postoperative pancreatic fistula following distal pancreatectomy.

Methods: This is a non-randomized controlled clinical study at a tertiary centre in China. The major eligibility criterion is the presence of lesions planned for distal pancreatectomy. The pancreas will be ligated at 5 mm from the pancreatic stump with a quantified force to provide a pancreatic duct burst pressure of approximately 40-70 mmHg. The pancreas will be severed using energy-based devices before or after the ligation. Postoperative regular follow-up will be performed. The primary outcomes includes postoperative pancreatic fistula and postoperative hospital stay, and the secondary outcomes includes intra-abdominal infection, incision infection, and postoperative treatment costs. The primary outcomes and secondary outcomes of patients in this cohort will be statistically compared using appropriate tests.

Results: The study started in Feb 2025 and the recruiting time is from Feb 2025 to Sep 2025.

Conclusions: This protocol proposes a novel approach for pancreatic stump management aimed at preventing postoperative pancreatic fistula following distal pancreatectomy. The research team established the optimal ligation force for the pancreatic stump to ensure adequate burst pressure for the pancreatic duct while preventing acute stump necrosis, thereby theoretically reducing the risk of postoperative pancreatic fistula. Clinical Trial: ChiCTR.org Registry ChiCTR2500097781;https://www.chictr.org.cn/showproj.html?proj=247008

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Ligation of pancreatic stump with quantified force during distal pancreatectomy for postoperative pancreatic fistula: study protocol for a single center non-randomized controlled clinical study.

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Abstract

Background: The closure of pancreatic stump after distal pancreatectomy remains controversial. Currently, the main methods of pancreatic stump closure include manual suturing and stapler closure. However, both methods carry a high risk of postoperative pancreatic fistula, which may be associated with the difficulty of balancing the provision of sufficient pancreatic duct burst pressure and ensuring blood supply to the stump.

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Trial registration: ChiCTR.org Registry ChiCTR2500097781;https://www.chictr.org.cn/showproj.html?proj=247008

Keywords: Pancreatic surgery, Distal pancreatectomy, Pancreatic stump ligation, Quantified ligation force, Postoperative pancreatic fistula

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Introduction

Distal pancreatectomy (DP) is a fundamental surgical procedure for treating inflammatory lesions, benign and malignant tumors in the pancreatic body and tail. Postoperative pancreatic fistula (POPF) is a common and severe complication of DP, with an incidence rate of approximately 30-50%[1 2]. POPF can lead to delayed gastric emptying (DGE), intestinal obstruction, hemorrhage, wound infection, intra-abdominal abscess, and sepsis. These complications can further increase hospital stay and medical expenses, and may potentially result in death[3 4].

To reduce POPF, surgeons have explored numerous strategies, aiming to achieve better outcomes through improved patient management and advancing techniques[5-10]. The closure technique of the stump is a crucial factor influencing the occurrence of POPF, primarily including two mainstream methods: manual suturing and stapling closure[5 6]. Stapling devices are often used due to their simplicity and convenience, but they may not effectively close the pancreatic stump when the pancreas is hard or thick. In such cases, manual suturing often becomes the only option. Additionally, surgeons have investigated techniques such as wrapping the stump with mesh[7], saline-coupled radiofrequency ablation[10], pancreaticojejunostomy[9], preoperative pancreatic duct stenting[11 12], and the application of fibrin patches to the stump[8]. Unfortunately, none of these techniques have significantly reduced the risk of pancreatic fistula. In 2022, the International Study Group on Pancreatic Surgery (ISGPS) stated in their expert consensus on the management of the pancreatic stump during distal pancreatectomy that both manual suturing and stapling closure have their respective advantages, and there is no difference in the risk of pancreatic fistula between the two methods. The use of energy devices or additional biomaterials to seal the pancreas, or the combined use of the methods, does not reduce the incidence of pancreatic fistula[13].

The key to preventing pancreatic fistula lies in the closure of the main pancreatic duct (MPD). The issue with stapling closure is that it may not provide a sufficiently high burst pressure for the pancreatic duct, even when the pancreatic stump is well-closed. Under physiological conditions, the pancreatic duct pressure ranges from 3-31 mmHg[14 15], but approximately half of the burst pressures provided by stapling devices for pancreatic duct closure are below 31 mmHg[16 17], leading to pancreatic fistula in some patients. Manual suturing can provide a burst pressure of up to 400 mmHg for the pancreatic duct through sutures, but the high pressure on

the tissue can cause tissue necrosis and new pancreatic duct proliferation, resulting in pancreatic fistula[17]. Additionally, it can be difficult to locate the main pancreatic duct after pancreatic transection in some patients, and empirical suturing increases the risk of pancreatic fistula.

Ligating the pancreatic stump is another closure technique of the pancreatic stump. By ligating the pancreatic tissue proximal to the stump, it can provide sufficient burst pressure for the pancreatic duct. However, ligation may also lead to acute tissue necrosis and pancreatic duct regeneration, similar to suturing[18]. To address this issue, the project applicant quantified the ligation force to achieve a burst pressure of approximately 40-70mmHg for the pancreatic duct. The blast pressure is much higher than the maximum pressure of the pancreatic duct under physiological conditions, but lower than the average arterial pressure under physiological conditions. Therefore, theoretically, it can avoid direct leakage of pancreatic juice from the pancreatic duct while reducing the risk of pancreatic stump acute necrosis by providing partial blood supply to the pancreatic stump, which prevent POPF caused by the necrosis-proliferation process of the pancreatic stump.

To validate the hypothesis, we launched the current clinical trial. According to the Evidence Map of Pancreatic Surgery (https://www.evidencemap.surgery/), this is the first trial of its kind[19].

Methods

The methods have been designed and are reported according to the SPIRIT reporting guidelines[20].

Study setting

This is a non-randomized controlled clinical study at a tertiary centre in China. Experienced surgeons will determine the eligibility of their patients and obtain informed consent form (see online supplemental materials). Patients who are scheduled to undergo distal pancreatectomy will be included in this study. An overview of the protocol is shown in figure 1.

Endpoints

Primary endpoints:

POPF

Postoperative hospital stay

Secondary endpoints:

Intra-abdominal infection

Incision infection

Postoperative treatment costs

Definition

In this study, POPF adopts the definition proposed by the International Study Group of Pancreatic Surgery. Intra-abdominal infection and incision infection 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 criteria:

1. Patients fully understand this study, voluntarily participate, and sign the Informed Consent Form (ICF);

2. Age between 18 and 75 years old;

3. Planned for distal pancreatectomy (including body and tail of the pancreas);

4. The intended pancreatic transection line is located on the left side of the portal vein.

Exclusion criteria:

1.History of previous pancreatic surgery;

2.Additional surgical procedures required for the residual pancreas;

3.Proximal pancreatic duct obstruction, with planned anastomosis between the residual pancreas and the digestive tract;

4.Use of long-acting somatostatin analogues during the perioperative period;

5.Patients who are judged by the investigator to be unsuitable for participation in this study.

Group allocation

Patients will be allocated to the experimental group or the control group according to their voluntary choice. Recruitment will be discontinued for any group upon reaching the predefined sample size.

Study interventions

Evaluation of the texture of the pancreas: After baseline visit and admission, eligible participants will be judged by the surgeon and the first assistant in terms of the texture of the pancreas (soft, medium, hard) during

the operation. If the two disagree, a third surgeon will be invited to make the decision.

Ligation of the pancreatic stump for experimental group: The pancreas will be ligated at 5 mm from the pancreatic stump before or after severing the pancreas. To achieve the proper ligation force, a predetermined force will be generated with a force device outside the body, and record the deformation length of the implantable silicone/rubber. When performing ligation in vivo, the specific ligation force is reproduced by reproducing the deformation length measured in vitro.

Pancreatic stump management for control group: The pancreatic stump will be managed by manual suturing or stapling closure according to the surgeon's clinical judgment and preference.

Distal pancreatectomy: Distal pancreatectomy will be performed according to the standard process.

Postoperative management: General clinical treatment will be conducted in both two groups. The patient's body temperature and drainage volume will be recorded daily. The amount and the amylase concentration of the drainage fluid as well as the blood will be routinely measured. Drains will not be removed before POD 3. After POD 3, drains will be left in place until either the amylase concentration was less than 3X the upper limit of normal serum amylase concentration, or the output was less than 20 mL/day with the amylase concentration less than 3, 000 U/L, or the out put was less than 5mL/day.

Follow-up: For the 3 months after surgery, patients should maintain a regular follow-up session every 2 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), and recent medical interventions. Laboratory tests and imaging examinations will be done at the surgeon's discretion.

Statistical methods

1. Hypothesis

Null hypothesis: The rate of POPF in patients who undergo pancreatic stump ligation is not less than that using other closure techniques.

Alternative hypothesis: The rate of POPF in patients who undergo pancreatic stump ligation is less than that using other closure techniques.

2. Sample size calculation

Based on published clinical studies on the incidence of pancreatic fistula using other closure techniques, the incidence of POPF was set at 40%. According to the results of previous animal experiments, the expected incidence of POPF in the ligation strategy is 5%. Using the formula of $n=2\acute{p}\acute{q}\left(Z a_{\alpha}+Z_{\beta}\right)^{2}/\left(p1-p2\right)^{2}$ for sample size calculation with the probability of type I error of 0.05 and the statistical power of 0.90, It is estimated that 30 participants should be included in each group.

3. Statistical analysis

All statistical analyses will be conducted using SAS 9.3 software. Generally, normality tests will be conducted for measurement data, describing the mean, standard deviation, or median, quartiles, minimum, and maximum values based on the distribution type. The count data will describe the number and percentage of cases in each category. The rate effect indicator will calculate the effective rate and 95% confidence interval. Missing values will not be filled in for research purposes, and will not be included in the calculation of percentages unless otherwise specified.

Results

The version number and date of the protocol are v2.0 and January 22, 2025, respectively.Recruitment of participants for the study commenced in February 2025 and will conclude when the estimated sample size has been included (in or around September 2025) and the follow-up has been finished (in or around December 2025).

Discussion

POPF remains an unresolved issue after distal pancreatectomy[13 21]. Currently, stump closure techniques primarily include manual suturing and stapling, both of which carry a high risk of POPF. Animal studies suggest that the key to POPF after distal pancreatectomy may lie in the difficulty of balancing pancreatic duct burst pressure and pancreatic tissue necrosis. We attempt to address this by ligating the pancreatic stump with proper force.

Although suturing the main pancreatic duct has been shown to reduce the risk of POPF[22 23], it is difficult to ligate due to its location within the pancreatic parenchyma, and the main pancreatic duct is often difficult to

locate during surgery. Therefore, the adopted method involves ligating the pancreatic stump rather than the MPD. Animal studies have demonstrated that ligation or similar techniques can provide sufficient burst pressure for the pancreatic duct. However, similar to manual suturing, excessive ligation force can lead to pancreatic tissue necrosis[18]. Through experiments on specimens from patients with pancreatic space-occupying lesions, we found that the conventional knotting force applied by surgeons ranges from 10-14 N, corresponding to a pancreatic duct burst pressure exceeding 400mmHg. This burst pressure is not only significantly higher than the maximum pressure of the pancreatic duct under physiological conditions but also exceeds the mean arterial pressure. For pancreas with soft, medium, and hard textures, ligation forces of 2.5 N using 4 strands of 0 silk braided non-absorbable suture are sufficient to achieve a pancreatic duct burst pressure of 40-70mmHg. This pressure is lower than the mean arterial pressure, theoretically minimizing the impact on blood supply to the pancreatic stump and reducing the risk of acute pancreatic tissue necrosis, and consequently it lowers the risk of POPF caused by the necrosis-proliferation process of the pancreatic stump. Therefore, we initiated a prospective clinical study on this pancreatic stump treatment technique, which quantifies the ligation force. The aim of the study is to determine whether this approach can reduce the risk of POPF and provide new insights into pancreatic stump closure.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. 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.

Strengths and limitations of this study

1. A prospective design to assess a new strategy for managing the pancreatic stump during distal pancreatectomy.
2. The new strategy provides a sufficiently high pancreatic duct blast pressure with preserving partial blood supply to the pancreatic stump.

3. The non-randomized design of the study.

Provenance and peer review: Not commissioned; externally peer reviewed.

List of abbreviations

DP: Distal pancreatectomy;

POPF: Postoperative pancreatic fistula;

DGE: delayed gastric emptying;

ISGPS: the International Study Group on Pancreatic Surgery;

MPD: the main pancreatic duct;

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials;

CTCAE: Common Terminology Criteria for Adverse Event;

ICF: Informed Consent Form.

POD: Postoperative Day

Declarations

Ethics approval and consent to participate: Written informed consent from all the patients screened will be obtained before the procedures start. Before deciding whether to participate,the participants aged 18 to 75 will be explain carefully about the background, purpose, methods, potential benefits, risks, and inconveniences associated with this study, as well as their rights as a participant. Any questions will be patiently answer by the research team to ensure they understand the content as fully as possible. Participation in this study is entirely voluntary and the signing of the consent form shall be done by the individual themselves, or their parents, or their legal guardian. The study has been approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology(2024-0833-02). The results of the study will be published in an international peer-reviewed journal. The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki.

Consent for publication: A model informed consent form has been provided and uploaded as an additional file upon submission.

Availability of data and materials: 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.The full trial

protocol and informed consent materials are available at any reasonable request to the corresponding author.

*Competing interests:*None declared.

*Funding:*None.

*Authors' contributions:*SG, HW and TY participated in creating the study design. LC, JX, MY and YY drafted the manuscript. SG, HW and TY provided a critical revision of the manuscript. All the authors read and approved the final manuscript.

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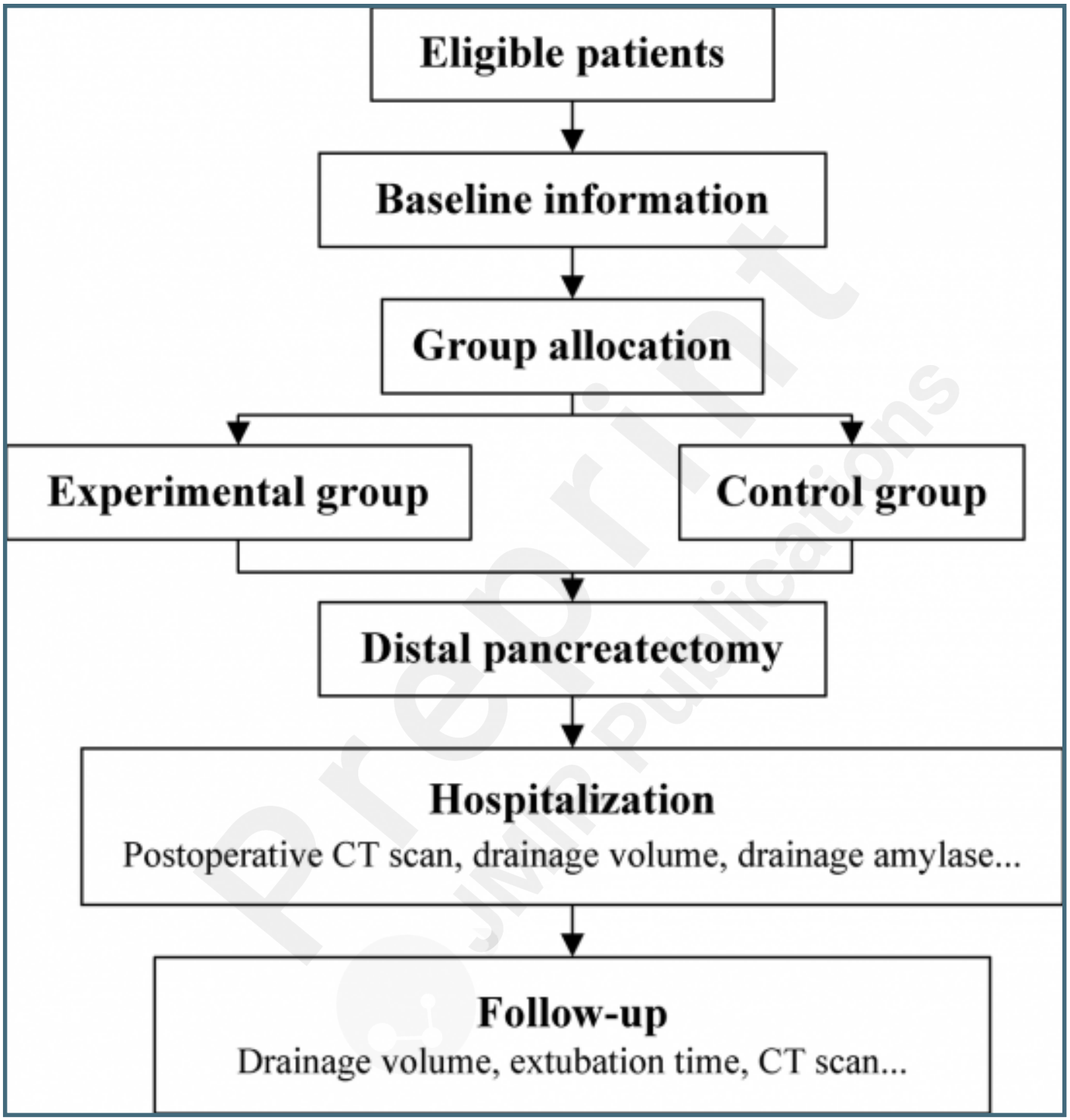
Figure legend

Figure 1. Flow chart of the study.

Supplementary Files

Figures

Flow chart of the study.



CONSORT (or other) checklists

SPIRIT checklist.
URL: http://asset.jmir.pub/assets/5958e76055c18d89c2bd33ef6ae66a7a.pdf