

STUDY PROTOCOL

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Indocyanine green fluorescence in the evaluation of post-resection pancreatic remnant perfusion after a pancreaticoduodenectomy: a clinical study protocol

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Abstract

Background Pancreaticoduodenectomy is associated with an incidence of postoperative complications of approximately 41%. One of the most severe complications is a postoperative pancreatic fistula. The exact cause of postoperative fistula development is still unknown, but it appears to be multifactorial. Proper perfusion of pancreatic remnant is essential for the healing of pancreaticojejunostomy. To date, there is no method to reliably evaluate the vascular supply of the remnant. One of the methods for the assessment of organ perfusion is the indocyanine green fluorescence. This study aims to determine if indocyanine green fluorescence is a reliable method to measure the perfusion of the post-resection pancreatic remnant. The secondary outcome is to determine if intraoperative evaluation of the vascular supply of the post-resection remnant may predict the increased risk of postoperative pancreatic fistula development.

Methods This study is designed as a prospective, observational study. All consecutive patients undergoing open or robotic pancreaticoduodenectomies at our department during the 1st May 2024–31st December 2026 period will be enrolled. The exclusion criteria are an allergy to indocyanine green and refusal by the patient. The adequacy of the vascular supply of the post-resection pancreatic remnant will be intraoperatively evaluated using a fluorescence detector. Patients will be divided into two groups: Those with high risk of pancreatic fistula development and those with low risk. The incidence of pancreatic fistulas in both groups is to be compared. Postoperative data including morbidity, mortality, hospital stay, intensive care unit stay and postoperative fistula development will be collected.

Discussion If an intraoperative assessment of the perfusion of post-resection pancreatic remnant using indocyanine green is proven to be a suitable method to estimate the increased risk of the pancreatic fistula, the list of the existing known risk factors could be expanded. In the most high-risk patients the modification of the surgical procedure could be considered.

Trial registration Number: NCT06198400 ClinicalTrials.Gov. Date 08.01.2024.

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Keywords Pancreatic surgery, ICG, Minimal invasive surgery, Pancreatic cancer, Pancreatic perfusion, Prospective study

Background

Pancreatic cancer is the seventh leading cause of cancer-related deaths worldwide with an average five-year survival rate of below 5% [1, 2]. Pancreatoduodenectomy carries a high risk of postoperative complications. According to some studies, the morbidity rate is around 41% [3, 4]. One of the most severe complications of pancreatic resection is the postoperative pancreatic fistula (POPF). POPF remains a major cause of morbidity and mortality [5]. It prolongs the length of stay, reduces quality of life, and increases the rate of re-operations and hospital costs [6]. Patients in need of postoperative oncological therapy have worse oncological outcomes [7]. POPF rates after pancreaticoduodenectomy (PD) is reported to be 21.3% [6]. According to updated classification by the International Study Group of Pancreatic Fistula, POPF is redefined to three categories: a biochemical leak with little or no clinical significance (formerly POPF grade A), grade B, and grade C. Grade B requires a change in postoperative management while grade C POPF refers to those postoperative pancreatic fistulas that require reoperation or lead to single or multiple organ failure and/or mortality attributable to the pancreatic fistula [8]. POPF grade C incidence is 3.5% with a high mortality rate of around 25% [6].

Although studies from the end of the last century confirmed the necessity of a sufficient vascular supply of the post-resection pancreatic remnant for proper

healing of the pancreaticojejunostomy so far, only a few studies have addressed this issue [9]. The pancreas is a well-perfused organ with varying pancreatic perfusion between 38.4 mL/min/100 mL and 356 mL/min/100 mL [10]. Macroscopic evaluation of the blood perfusion of the pancreatic remnant might be difficult to objectively assess and may be a source of bias by subjective interpretation. One of the methods for organ perfusion measurement with recent expansion is the application of Indocyanine green fluorescence (ICG) [11]. ICG is a fluorescent dye, and the principle of fluorescence is the emission of energy in a very short time caused by the effect of radiation. The method was first used in the 1950s [12]. Currently, ICG is routinely used in visceral surgery for the objective measurement of blood flow of the colonic stump and colorectal anastomosis [13, 14]. A recent, extensive systematic review showed the potential reduction of colorectal anastomotic leak incidence when ICG was perioperatively used [15]. The application of ICG in pancreatic surgery is much less explored, and there are only few studies urging development of a prospective study [16–18].

The main outcome of this study is to determine the possible utilisation of ICG in the assessment of pancreatic remnant perfusion. The secondary outcome is to evaluate if an intraoperative assessment of the vascular supply of the post-resection remnant may predict the increased risk for POPF development.

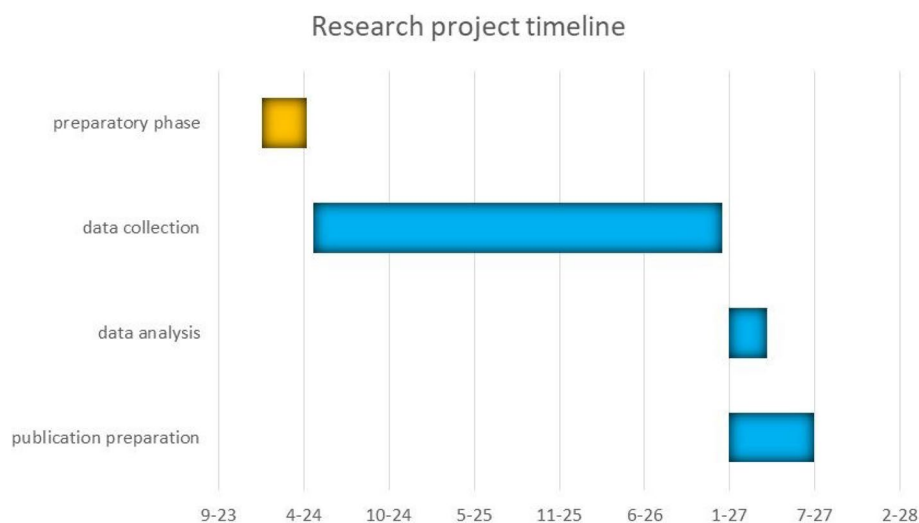


Fig. 1 Timeline of the project

Methods

This study is designed as a prospective observational study. All consecutive patients undergoing PD at our institution in the 1.5.2024–31.12.2026 period will be enrolled in this study (Fig. 1). Exclusion criteria are: patients with an allergy to ICG and a refusal to enrol in the study. The data on all known risks of POPF development will be preoperatively and intraoperatively collected. During the operation, the data about the texture of the gland and thickness of the pancreatic duct will be collected. Soft tissue of the gland and pancreatic duct diameter ≤ 3 mm will be considered as independent risk factors [19]. Other risk factors of POPF development that will be monitored are perioperative blood loss, transfusion administration, age, and body mass index [20, 21]. Cut-off values are blood loss of more than 1,000 mL, administration of any transfusion perioperatively, age of more than 70 years and body mass index over 25 [21]. For risk stratification a 10-point scoring system will be used [22]. To prevent risk of bias a single pancreatic team will perform all resections with a single specific technique. A standard open or robotic Whipple procedure will be performed. Antibiotic prophylaxis will be applied according to a standardised protocol. For the reconstruction one-loop pancreaticojejunal anastomosis, hepaticojejunal anastomosis and gastrointestinal anastomosis will be performed. In the open Whipple the uniformed duct-to-mucosa technique of PJA will be used with single-monofilament absorbable PDS 4/0 or 5/0 stitches. For the robotic Whipple, the Blumgart technique will be used. A nasojejunal tube will be routinely placed along with a nasogastric tube during an open Whipple procedure. Each patient will get abdominal drainage placed near the PJA. A standard lymphadenectomy will be performed in oncological patients. The adequacy of the vascular supply of the post-resection pancreatic remnant will be evaluated intraoperatively. Indocyanine green fluorescence product -*Verdyne*TM will be applied intravenously immediately after pancreatic neck resection. Perfusion of remnant will be evaluated visually by the surgical team using ICG detector. Patients will be divided into two groups: Those with high risk of pancreatic fistula development and those with low risk. The multivariate analysis will help to eliminate differences between the patients. Using a combination of these methods, the risk of bias can be considered minimal. The null hypothesis presumes that the incidence of POPF after PD will not differ in both groups.

Discussion

Many studies attempting to reduce the incidence of POPF can be found in the literature review. These are modifications of the anastomosis construction technique,

the application of tissue adhesives, the use of stents, or the primary performance of preventive total pancreatectomy in high-risk patients [6, 23]. One of the main premises for an uncomplicated healing of PJA is adequate vascular supply and proper perfusion of the area [9]. In native form, the area of the neck of the pancreas where the pancreaticojejunal anastomosis (PJA) is constructed, is supplied by pancreaticoduodenal arteries and a highly-variable dorsal pancreatic artery [9]. During the PD, the head of the pancreas is resected and the superior and inferior pancreaticoduodenal arteries are cut. Therefore, the proximal part of the post-resection pancreatic remnant after resection is supplied only by the right branch of the dorsal pancreatic artery. In recent studies we described a group of patients with a potentially hazardous anatomical arrangement of supplying arteries. In 32% of patients the dorsal pancreatic artery lies directly in line with the resection or is even completely missing [24]. In this group of patients, the post-resection pancreatic remnant seems to be perfused only by inconsistent anastomoses between the splenic artery and the left branch of the dorsal pancreatic artery [24]. Such anatomical arrangement may imply a higher risk of PJA-insufficiency with an elevated risk of POPF development. Strasberg observed in his study, vascular supply and perfusion of pancreatic remnants in patients during the 123 pancreaticoduodenectomies [9]. Perfusion was assessed clinically and by Doppler ultrasound. In case of impaired perfusion of the pancreatic remnant, re-resection was performed until adequate perfusion was ensured. Using this optimization, he was able to reduce the POPF rate after PD to 1,6% (2/123) [9]. In conclusion, proper suturing technique and a focus on adequate perfusion and vascular supply of the pancreatic remnant with its intraoperative optimisation can reduce incidence of POPF [9]. To date, there is no strong data from studies that attempt to intraoperatively evaluate the vascular supply of the remnant. Only one case study using ICG for evaluation of the blood flow in the post-resection remnant has been published [17]. In addition, the need for the introduction of new studies devoted to this issue is emphasised by many authors [17, 18, 23, 25].

For this reason, the need to create a study focusing on this issue is obvious. The results can be used by surgeons in the intraoperative decision-making process to reduce the number of postoperative complications. Re-resection of the pancreatic remnant as Strasberg et al. [9] did in his study with excellent results is one possible method. Eventually, a total pancreatectomy is the uttermost method of POPF prevention in the highest risk patients.

The proposed study has some limitations of which we are aware. First, it is a single-center, observational study designed in such a manner preventing it from

randomization. The matching may be difficult due to a relatively-large number of individual factors intended for the cross-matching. This is related to the heterogeneity of a group of patients undergoing the PD. The main indication for resection in our group will be adenocarcinoma in the head of the pancreas. Other pathologies such as chronic pancreatitis, neuroendocrine tumours and intraductal papillary mucinous neoplasms will be also included in the study. We are convinced that despite its limitations, we might get some promising information about the perfusion of pancreatic remnants. Despite all the pre-existing limitations, we maximised every measure possible to eliminate potential bias through the department of biostatistics. In the future, we are planning to follow up with further studies with regard to the primary outcome of this study.

Trial status

Date: 06.05.2024.

First version of the manuscript.

Date recruitment and completion: 1.5.2024–31.12.2026.

Abbreviations

| | |
|------|----------------------------------|
| ICG | Indocyanine green |
| PD | Pancreaticoduodenectomy |
| POPF | Postoperative Pancreatic Fistula |
| PJA | Pancreaticojejunal anastomosis |
| DPA | Dorsal pancreatic artery |

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Authors' contributions

Štěpán-Ota Schütz is a postgraduate student at Charles University in Prague in the field of experimental surgery. The theme of the PhD thesis focuses on the vascular supply of the post-resection pancreatic remnant with a focus on ICG application. He registered the study and prepared the study protocol. He will perform experiments, and collect the data. He will be in charge of the graphic side of the project. He will participate in the preparation of data publication. Michael Rousek designed the project. He will coordinate all of the team members. He will perform the surgeries, perform the experiments and he will interpret the data results. He will prepare the results for publication. Pavel Záruba will perform the surgeries and experiments. He will participate in the preparation of data publication. Tereza Husárová is a postgraduate student at Charles University in Prague in the field of experimental surgery. The theme of the PhD thesis focuses on use of modern diagnostic methods in hepatobiliary and pancreatic surgery. She participated in preparations of the study protocol and will collect the data. Radek Pohnán will help with data collection and interpretation. He will act as a consultant for partial tasks of the project. He will participate in the preparation of data publication.

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Availability of data and materials

Not applicable.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Central Military Hospital in Prague and informed consent to participate was obtained from participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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