Study Protocol

Pylorus resection versus pylorus preservation in pancreatoduodenectomy: A multicenter surgical registry-based randomized active-controlled trial (RRCT) from the German DGAV StuDoQ|Pancreas Registry

PyloResPres-TRIAL

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Zusammenfassung

Im Rahmen einer partiellen Pankreatoduodenktomie (PD) werden zwei unterschiedliche Strategien bei der Durchtrennung der Magen-Darmpassage oralwärts angewendet. Dies ist zum einen die Resektion (prPD) und zum anderen der Erhalt (ppPD) des Magenpförtners (Pylorus). Die verzögerte Magenentleerung (DGE) nach PD ist eine ernstzunehmende Komplikation, die nach Verfolgung beider Strategien (ppPD oder prPD) auftreten kann. Vorhandene Metaanalysen, die das DGE nach Durchführung einer der beiden Verfahren untersuchen, kommen nach wie vor zu gegensätzlichen Ergebnissen. Grosse, multizentrisch-randomisiert-kontrollierte Studien (RCT) zu diesem Thema existieren nicht. Durch die vorliegende Studie soll nun genau dieser Mangel behoben werden. In einer prospektiv-multizentrischen und Register-basierten randomisiert kontrollierten Studie (RRCT), soll die Effektivität der ppPD mit der der prPD in der deutschen flächendeckenden Realität verglichen werden. Dieses neuartige Studiendesign erlaubt eine bessere Übertragbarkeit der Ergebnisse. Im Vergleich zu konventionellen RCT's ist hier mit geringeren Kosten, einer schnelleren Rekrutierung der notwendigen Patientenzahlen und potentiell vollständigeren Follw-up Daten zu rechnen. Die deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) hat ein qualitativ hochwertiges nationales Pankreasregister (StuDoQ|PanKreas) etabliert. Dieses soll der Qualitätskontrolle, Risikobeurteilung und Ergebnisuntersuchungen in der Pankreaschirugie dienen. In genau dieses Register wird der vorliegende RCT eingebettet. Eingeschlossen werden alle Patienten ≥18 Jahre, bei denen eine partielle Pankreatoduodenektomie sowohl bei benignen als auch maligen Erkrankungen geplant ist. Der primäre Endpunkt ist der Unterschied in der Inzidenz des DGE innerhalb der ersten 30 Tage nach Indexoperation. Die sekundären Endpunkte sind die 30 -Tages Mortalität, Morbidität, Blutverlust, Krankenhausverweildauer, Anastomoseninsuffizienzen und OP-Zeit. Insgesamt sollen 982 Patienten durch ein zwei stufiges Gruppen-sequentielles Design randomisiert werden. Durch diese Studie soll letztendlich die Frage beantwortet werden, welches der beiden Verfahren in Zukunft zur Reduktion des DGE evidenzbasiert eingesetzt werden soll.

Abstract

Background

Pancreatoduodenectomy (PD) is the treatment of choice for various benign and malignant tumors of the pancreatic head or the periampullary region. Besides the classic Whipple procedure including distal gastrectomy, two PD variants exist, with or without pylorus resection but preservation of the stomach. In pancreatic surgery DGE remains a serious complication after resection [7, 26] with an incidence varying from 4.5% to 45% [1], potentially delaying further treatment. No high-quality patient- and observer-blinded, large multicenter RCTs for German patients exist aiming to prove or disprove the superiority of prPD compared to ppPD for reducing DGE or other relevant complications.

Therefore, this prospective multicentre registry-based RCT (RRCT) aims to investigate the effect of pylorus resection on DGE in PD in a German real world setting. It further allows enhanced generalisability of findings, low costs, rapid consecutive enrollment and the potential completeness of follow-up for the reference population.

Methods/Design

The German Society for General and Visceral Surgery (DGAV) established the high-quality national pancreatic surgery registry (StuDoQ|Pancreas) for quality control, risk assessment and outcomes research in pancreatic surgery in which the RCT will be embedded. The trial includes patients ≥18 years of age scheduled for PD for any indication. Primary endpoint is the difference in incidence of DGE within 30 days. The secondary endpoints are 30-day mortality, morbidity, blood loss, hospital stay, anastomotic insufficiency, operation time, and initiation of an adjuvant therapy in cancer patients. A total of 982 patients will be randomized for prPP or ppPD using a two-stage group- sequential design.

Discussion

DGE is a relevant clinical problem following PD with a great impact on patients' recovery, length of hospital stay, Quality of life (QoL) and consecutive adjuvant therapies. As there is no causal therapy, prevention of DGE is essential to improve outcome. Therefore, this pragmatic multicentre registry-based randomized RCT (RRCT) is to investigate ppPD vs prPD and to provide the needed evidence to decide which resection strategy should be applied

Background

Pancreatoduodenectomy (PD) is the treatment of choice for various benign and malignant tumors of the pancreatic head or the periampullary region [2,3]. Besides the classic Whipple procedure including distal gastrectomy, two PD variants exist, with or without pylorus resection but preservation of the stomach [4]. The pylorus preserving pancreatoduodenectomy (ppPD) showed comparable results with regard to long-term survival, surgical mortality and tumour recurrence when compared to the classical PD with resection of the pylorus (prPD) [5]. Pancreatic surgery has specific complications, but recent developments in postoperative patient management have led to continuous improvement in outcomes [6,7]. Nevertheless, DGE remains a serious complication after resection [7, 26] with an incidence varying from 4.5% to 45% [1]. DGE impairs postoperative recovery and quality of life, which generally delays or omits adjuvant chemotherapy with a negative impact on survival [8]. DGE is believed to be a functional impairment of the physiological propulsive action of the stomach and especially the pylorus. Therefore, some patients react well to propulsive medication such as erythromycin [9].

No high-quality patient- and observer-blinded, large multicenter RCTs for German patients exist aiming to prove or disprove the superiority of prPD compared to ppPD for reducing DGE or other relevant complications. A recent meta-analyses [19] is not conclusive regarding existing or lacking effects (95% aggregated CI [0.57; 4.47]). In order to make the meta-analysis sufficiently precise, evidence from a large trial is needed.

Furthermore, delayed gastric emptying after PD as a consequence of pancreatic fistula has not been addressed in former trials in detail.

Up to now, several studies showed comparable morbidity and mortality in both surgical groups so that both seem to be safely performable [10-13].

Therefore, the results of the PyloResPres trial will have impact on the strategy of pancreatic head resections (i.e., comparative effectiveness of resecting vs pylorus preserving) and by this, may offer an option to reduce the risk of DGE.

Methods

Participants / Study Population

Any patient aged 18 years or older scheduled for PD for any indication with written informed consent is eligible. Only patients in which a classical Whipple procedure needs to be performed, patients who participate in another intervention trial interfering with the surgical intervention or the outcome of this trial, as well as patients with expected lack of compliance and/or irreconcilable language barriers will be excluded. By the defined less stringent eligibility criteria almost the whole spectrum of pancreatic surgery is of interest. This population is covered by the StuDoQ|Pancreas Registry which provides representative data on pancreatic surgery in academic and non-academic institutions with a medium to high institutional or surgeon caseload, and acceptable morbidity and mortality [24]. The registry does not represent pancreatic surgery in the low-volume setting [14]. Using the existing high-quality StuDoQ|Pancreas infrastructure, this RRCT will be carried out in a real-world setting with many sites throughout Germany being involved expecting a rapid consecutive enrolment. Therefore, the results will be of great clinical impact and have an enhanced generalisability of findings.

Randomization

All patients admitted will be consecutively screened, and all eligible patients will be included after initiation of the study. Patients will be allocated by concealed randomization at the day of the index surgery using the internet-based tool '*Randoulette*' (https://wwwapp.ibe.med.uni-muenchen.de/randoulette/) for all participating institutions to achieve comparable treatment groups. The randomization to both treatments (ppPD, prPD) will be performed with a 1:1 allocation ratio and is based on a permuted balanced block design considering stratification by site.

Treatments / Procedures

In this trial the effectiveness of two established and routinely performed surgical procedures (ppPD vs. prPD) will be compared. In both groups, open partial PD will be carried out in accordance to the local standardized approach. In brief, after reconstruction of a pancreatic anastomosis (pancreatojejunostomy or pancreatogastrostomy) and a hepaticojejunostomy, the duodenum will be divided at least 1cm distal to the pylorus for the pylorus preserving group (ppPP), preserving the

gastric vessels along the lesser and the greater curvature. An antecolic or retrocolic end-to-side duodenojejunostomy will then be performed. In the pylorus resecting group (prPD), the stomach will be resected within 5 cm proximal to the pyloric ring with complete preservation of the gastric vessels along both curvatures to maintain perfusion of the distal stomach via the gastroepiploic vessels and the left gastric artery, respectively. Whether continuous or interrupted sutures are employed or whether the gastric staple line is included or excluded from the anastomosis in a prPD is left up to the standard at the respective surgical department. An antecolic or retrocolic end-to-side gastrojejunostomy will be performed. The route of reconstruction must be documented in the StuDoQ|Pancreas Registry.
The surgical site is documented by a photograph at the end of the reconstruction.

Medical treatment

Peri- and postoperative medical treatment including antibiotic medication, prokinetic drugs and octreotide analogons can be used according to the respective institutional standards, but must be documented in the StuDoQ|Pancreas Registry. Furthermore, endoscopic examination in case of DGE and management of nasogastric tubes can be performed, but must also be documented in the StuDoQ|Pancreas Registry. In both groups, the nasogastric tube (NGT) can be removed as soon as mechanical ventilation is stopped, but the decision remains up to the surgeon in charge. All patients will be further treated as it is routinely carried out in the respective department. Follow-up examinations are scheduled at day 7, 14 and 30 postoperatively. The study protocol is shown in Figure 1.

Study objectives

Primary efficacy endpoint is the frequency of postoperative DGE according to the international ISGPS definition (Table 1) 30 days after index operation, compared between the two intervention groups [15]. Key secondary endpoints are overall severe morbidity (Clavien Dindo classification<3b vs ≥3b) [16], blood loss (ml), 30 day mortality (death from any cause), postoperative hospital stay, insufficiency of the gastro/pylorojejunostomy, operation time, initiation of adjuvant chemotherapy in cancer patients

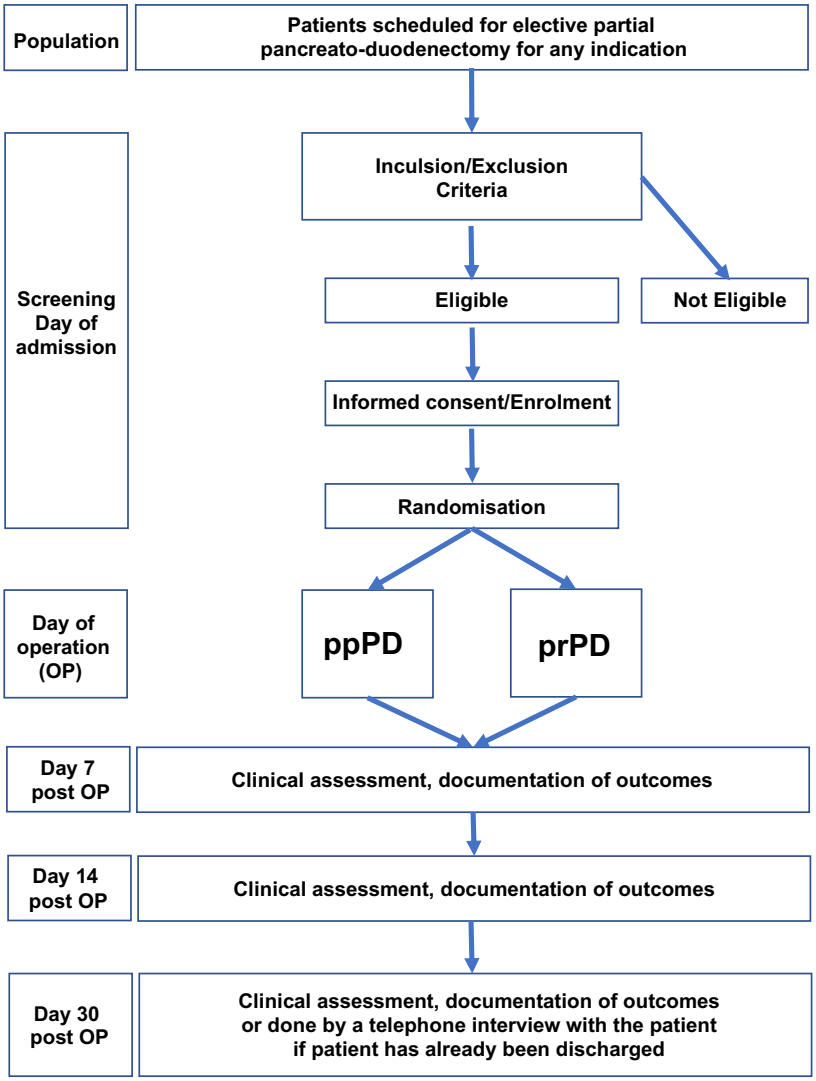

Figure 1
Flow chart of the PyloResPres study

Table 1
DGE (grading A-C) according to the ISGPS definition [15]3

Grade	Nasogastric tube	Solid food intake	Vomiting distension	Prokinetic medication
A	4-7d/reinsertion > d3	d7	±	±
B	8-14d/reinsertion > d7	d14	+	+
C	>14d/reinsertion > d14	d21	+	+

DGE, delayed gastric emptying; ISGPS, International Study Group for Pancreatic Surgery.

Methods against bias

Information bias

Due to the nature of the planned surgical interventions blinding of the surgeons is not possible. But, the assessment of DGE is objective. It uses the obvious criterion of the presence of a gastric tube as defined by ISGPS [1].

Selection bias

The setting of a registry based RCT allows to recruit patients from an unselected target population. It will also be possible to compare within the registry the in-study population with the out-of-study population. We also can apply statistical methods from surveys to extend the effects found in the study to the entire relevant StuDoQ|Pancreas Registry population.

Confounding

Randomization of patients will minimize selection bias and confounding variables. Correct randomization will be assessed by photograph which will be verified by the monitor (time and date of procedure). Both surgical procedures are standard procedures and regularly performed within the participating centres. Patients will be kept blind to the allocated and actually performed surgical procedure. Unblinding of the patients will be necessary in situations requiring reinterventions such as postoperative hemorrhage with the necessity of relaparotomy. Furthermore, the possible influence of the reconstruction route of the gastro/duodenojejunostomy, either retro- or antecolic, on DGE is a controversial issue in the literature. The antecolic route is said to induce less DGE [3,17,18]. Therefore, the reconstruction route must be documented in the StuDoQ|Pancreas Registry.

Sample size calculation

Sample size calculation was performed on the basis of the primary outcome “occurrence of DGE within 30 days after surgery”. The meta-analysis of RCTs presented in [19] gives an DGE rate of 18% (95% CI [13%; 23.4%]) for prPD and 21.5% (95% CI [15.6%; 27.1%]) for ppPD patients. Based on this and our goal to show a good effect for prPD compared to ppPD we choose the following planning scenario: an

absolute risk difference of 10% of DGE between both groups seems clinically relevant assuming 25% DGE risk in the ppPD group and 15% in the prPD group. We expect that for 15% of the patients in each group the corresponding DGE outcome cannot be assessed (e.g. due to dropout or mortality). In this case the binary efficacy outcome will be set to failure for the analysis. Therefore, for sample size calculation assumes a failure rate of 0.30 (=0.15+0.15) for the prPD and of 0.40 (=0.25+0.15) for the ppPD group.

A two-stage group sequential design is set up with an interim analysis after assessment of 50% of the sample size. Stopping is statistically based on rules derived from the primary interim result, however also based on the feasibility of patient accrual. This design avoids prolonged recruitment in order to reach statistical power if the goal is unachievable (the interim analysis cannot account for misspecification of the designing parameters that may emerge from the interim results) or if early significance can be claimed.

The critical values and the test characteristics of this group sequential test design were calculated for a Wang and Tsiatis design with boundary shape parameter Delta = 0.23. This Delta minimizes ASN_{H0} + ASN_{H01} + ASN_{H1} (average and expected sample size, respectively). For a specified significance level $\alpha = 0.05$ (two-sided) and rates $\pi_1 = 0.3$ and $\pi_2 = 0.4$ (odds ratio of 1.556) the power (1 - β) is 90.0% if the test stages consist of the sample sizes given in the last two columns of the table below (Fisher's exact test applied). The computation assumes an allocation ratio $(n_2/n_1) = 1.0$. This yields a total of 490.7+490.7 = 981.3 observations, resulting in a total number of 2 × 491 = 982 patients to be allocated to the trial.

The interim analysis will be performed after 246 patients randomized per group have been assessed (Software used: ADDPLAN® V 6.1.1).

A total number of 982 patients will be assigned to the trial taking into account 15% missing information with respect to DGE due to unspecific reasons. Assuming that about 75% of eligible patients consent to study participation about 1310 patients in total in accordance with site commitments have to be screened.

Documentation and data handling

Using the IT-infrastructure of the StuDoQ registries provides the following advantages: (1) Participation of institutions and documentation is already implemented; (2) The case report form is already established und implemented; (3) Additional and conditional parameters can be added at any time; (4) The data management (including consistency checks) is already established; (5) The study population can be reflected within the documented more general population increasing generalizability of the trial results. All patient data will be stored electronically in the StudDoQ pancreatic surgery registry. Following termination of the trial, data will be available for future use by participating canters of the registry.

As this trial is a registry-based study comparing two routinely performed surgical procedure adverse event (AE) management is not required. Therefore, a Data and Safeety and Monitoring Board (DSMB) is also not necessary.

Monitoring and quality assurance

A risk-based monitoring strategy will be applied in this study. The risk for GCP rule violations is estimated to be low as this trial is based on an existing registry to which centres are already contributing, inclusion criteria and interventions are simple and outcome criteria are clearly defined. Therefore, all trial sites will be visited after inclusion of 2 patients. Trial sites with relevant problems will be revisited within 3-6 months.

Discussion

DGE is a well-known complication in pancreatic surgery. Up to ISGPS's standardized definition of DGE in 2007 [15], it was not well defined [19-22], which led to non-comparable results between studies.

The hypothesis that prPD is superior to ppPD regarding a lower incidence of DGE is still controversially discussed [10,13,23]. As shown by Klaiber et al. [19], the meta-analysis of 8 observational studies provides quantitative estimates for a clear advantage for prPD compared to ppPD (OR 3.48, 95% CI [1.82, 6.67]). This has to be rated as no strong evidence since the trials have not been randomized. Additionally, for the non-randomized studies, a possible publication bias was present. The same paper [19] also shows a meta-analysis of three RCTs with an inconclusive result for

prPD (OR 1.60, 95% CI [0·57, 4·47]). A recent prospective single center study in Germany (PROPP trial) [13] gave a non-significant result but an effect estimate in the other direction (OR 0·75, 95% CI [0·39, 1·41]).

In line with these inconclusive results, the existing RCTs comparing ppPD and prPD have limitations arising from clinical and methodological heterogeneity. Postoperative morbidity and mortality were comparable in both groups. However, a Chinese meta-analysis [18] which evaluated the influence of pylorus removal on DGE showed a longer operation time, higher blood loss and higher mortality rate in the pylorus resecting group with no significant reduction in DGE. Limitations of this report were that three different resection types (prPD, Whipple resection and subtotal stomach preserving PD) were pooled together, and the majority of the analysed studies were non-RCTs.

Taking all these aspects together, we conclude that the question whether there is a difference in DGE after ppPD and prPD remains still unanswered. As no multicentre randomized controlled trial evaluating DGE between prPD and ppPD are available so far, there is need for such a large-scale trial in order to answer the question. Therefore, the objective of this pragmatic multicentre registry-based randomized RCT (RRCT) is to investigate ppPD vs prPD and to provide the needed evidence to make the meta-analyses conclusive. Therefore, the results of the PyloResPres trial will have impact on the strategy of pancreatic head resections (i.e., comparative effectiveness of resecting vs pylorus preserving) and by this, may offer an option to reduce the risk of DG.

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