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Prophylactic abdominal drainage after distal pancreatectomy (PANDORINA):
And international, multicentre, randomised controlled trial

Alberto Balduzzi

PhD thesis

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PROPHYLACTIC ABDOMINAL DRAINAGE AFTER DISTAL PANCREATECTOMY (PANDORINA): AN INTERNATIONAL, MULTICENTRE, RANDOMISED CONTROLLED TRIAL

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SUMMARY

Background: Attualmente, il posizionamento del drenaggio addominale dopo pancreatectomia distale (PD) è ritenuto lo standard di riferimento. Tale approccio è finalizzato a ridurre le complicanze legate alla formazione di fistole pancreatiche postoperatorie (POPF). Tuttavia, il valore aggiunto di questa prassi, soprattutto nei pazienti a basso rischio di sviluppare POPF, è oggetto di dibattito. Pertanto, abbiamo condotto uno studio mirato a valutare se l'adozione di una strategia senza drenaggio sia non inferiore in termini di risultati nei pazienti sottoposti a PD.

Methods: In questo studio multicentrico, randomizzato e controllato di non inferiorità internazionale, abbiamo arruolato pazienti sottoposti a PD elettiva in 12 centri nei Paesi Bassi e in Italia. I pazienti sono stati assegnati in modo casuale a “nessun drenaggio” o a “posizionamento di drenaggio”. È stata eseguita una stratificazione per pazienti a basso o alto rischio di POPF, in base al distal fistula risk-score (D-FRS). L'endpoint primario era la morbilità (punteggio Clavien-Dindo ≥3) e l'endpoint secondario più rilevante era lo sviluppo di POPF di grado B/C. L’analisi è stata condotta secondo intention-to-treat. Il margine di non inferiorità predefinito dell'8% è stato confrontato con il limite superiore dell'intervallo di confidenza (IC) al 95% a due code della differenza assoluta sia nell'endpoint primario che in quello secondario più rilevante. Le analisi dei sottogruppi si sono basate sul D-FRS. Questo studio è registrato presso il Registro dei Studi Clinici dei Paesi Bassi (NL9116).

Findings: Tra il 3 ottobre 2020 e il 28 aprile 2023, 282 pazienti sottoposti a PD sono stati randomizzati: 138 nel gruppo senza drenaggio e 144 nel gruppo con drenaggio. La morbilità maggiore è risultata comparabile tra i gruppi (21 [15,2%] vs 29 [20,1%],

differenza -4,9%, IC 95% da -13,77 a 3,97, $p_{non\text{-}inferiorità} = 0,002$). I tassi di POPF di grado B/C (16 [11,6%] vs 39 [27,1%], differenza -15,5%, IC 95% da -24,51 a -6,49, $p_{superiorità} <0,001$) e le complicanze complessive (46 pazienti, 33,3% vs 73 pazienti, 50,7%, p=0,003) erano entrambi inferiori nel gruppo senza drenaggio. I tassi di interventi radiologici e endoscopici postoperatori (14 pazienti, 10,1% vs 24 pazienti, 16,7%, p=0,109) e di re-interventi (6 pazienti, 4,4% vs 4 pazienti, 2,8%, p=0,476) erano comparabili tra i gruppi. Nel gruppo a basso rischio di POPF (n=81), il gruppo senza drenaggio aveva un tasso di morbilità maggiore inferiore (2 [4,5%] vs 7 [18,9%], differenza -14,4, IC 95% da -28,42 a -0,38, p=0,040). Nei gruppi a rischio intermedio ed elevato di POPF, la morbilità maggiore non differiva tra i gruppi.

Conclusion: Una politica senza drenaggio dopo PD non è inferiore al posizionamento di drenaggio in termini di morbilità maggiore ed è superiore in termini di riduzione della POPF di grado B/C che si è ridotta di oltre il 50%.

Funding: Ethicon UK (Johnson & Johnson Medical Limited, Edimburgo, Regno Unito).

ABSTRACT

Background: Prophylactic abdominal drainage is standard practice after distal pancreatectomy (DP). This approach aims to mitigate the consequences of postoperative pancreatic fistula (POPF) but its added value, especially in patients at low risk of POPF, is currently being debated. We aimed to assess the non-inferiority of a no-drain policy in patients after DP.

Methods: In this international, multicentre, randomised controlled non-inferiority trial, we recruited patients undergoing elective DP in 12 centres in the Netherlands and Italy. Patient were randomly assigned to either no drain or drain placement. Stratification was performed for patients at low or high risk of POPF, based on the DP fistula risk score (D-FRS). Primary outcome was major morbidity (Clavien-Dindo score ≥3) and the most relevant secondary outcome was grade B/C POPF. Analyses were performed by intention-to-treat. The predefined non-inferiority margin of 8% was compared with the upper limit of the two-sided 95% confidence interval (CI) of absolute difference in both the primary and most relevant secondary outcome. Subgroup analyses were based on the D-FRS. This trial is registered with the Netherlands Trial Registry (NL9116).

Findings: Between October 3, 2020 and April 28, 2023, 282 patients undergoing DP were randomised: 138 in the no-drain group and 144 in the drain group. Major morbidity was comparable between groups (21 [15·2%] vs 29 [20·1%], difference -4·9%, 95% CI -13·77 to 3·97, $p_{non\text{-}inferiority}$ = 0·002). The rates of grade B/C POPF (16 [11·6%] vs 39 [27·1%], difference -15·5%, 95% CI -24·51 to -6·49, $p_{superiority}$ <0·001) and overall complications (46 patients, 33·3% vs 73 patients, 50·7%, p=0·003) were both lower in the no-drain group. The rates of postoperative radiological and endoscopic interventions (14 patients, 10·1% vs 24 patients, 16·7%, p=0·109) and reoperations (6 patients,

4·4% vs 4 patients, 2·8%, p=0·476) were comparable between groups. In the low-risk POPF group (n=81), the no-drain group had a lower major morbidity rate (2 [4·5%] vs 7 [18·9%], difference -14·4, 95% CI -28·42 to -0·38, p=0·040). In the intermediate- and high-risk POPF groups, major morbidity did not differ between the groups.

Interpretation: A no-drain policy after DP is non-inferior to drain placement in terms of major morbidity and superior in terms of grade B/C POPF which was reduced by over 50%.

Funding: Ethicon UK (Johnson & Johnson Medical Limited, Edinburgh, UK).

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INTRODUCTION

Distal pancreatectomy (DP) is the standard surgical procedure for symptomatic benign, premalignant and malignant diseases in the left part of the pancreas. In about 25% of patients undergoing DP the postoperative course is complicated by postoperative pancreatic fistula (POPF) wherein pancreatic fluid with high levels of amylase leaks into the abdominal cavity. A POPF is considered a serious complication as it may give rise to post-pancreatectomy haemorrhage (PPH), intra-abdominal infected collections, and sepsis. To mitigate the clinical course of POPF after DP and prevent these secondary complications, prophylactic abdominal drainage is routine practice during DP.[1,2]

Some have argued that prophylactic abdominal drainage after DP can be omitted, especially in low-risk patients, as leaks are non-infected, unlike after a pancreatoduodenectomy where the intestinal tract is opened.[3] Moreover, a no-drain policy would free patients from the burden of a surgical drain and eliminate the risk of the drain actually facilitating infection with commensal skin flora and converting a self-limiting, contained collection, to a POPF.[4-7] Two systematic reviews of prophylactic abdominal drainage after DP have suggested that it is safe to omit drainage after DP but were mostly based on retrospective studies.[6,8] One multicentre randomised trial found comparable morbidity rates in patients after DP with or without abdominal drainage.[5] However, this trial did not stratify patients based on the risk of developing a POPF. This is relevant as the value and need for drainage may differ between patients at low and high risk of POPF.[9]

The lack of evidence is illustrated by the recent Brescia guidelines, which concluded that no specific recommendations on prophylactic abdominal drainage after DP could be made.[2] The present multicentre, randomised controlled non-inferiority PANDORINA trial was initiated with the primary objective to evaluate the hypothesis that a no-drain policy after DP does not worsen the risk of major morbidity (primary

outcome) and does not worsen the risk of POPF (most relevant secondary outcome).

METHODS

Study design

PANDORINA was an investigator-initiated, international, multicentre, randomised controlled non-inferiority trial comparing a no-drain policy with prophylactic abdominal drainage in patients after DP for (pre)malignant and non-malignant indications. The study protocol has been previously published, describing the rationale and design of the study.[10] The study was performed in 10 centres of the Dutch Pancreatic Cancer Group and two centres in Italy.

This trial complies with the principles of the Declaration of Helsinki and the CONSORT guidelines for randomised controlled trials[11] and is registered with the Netherlands Trial Registry (NL9116). The institutional review boards of all participating centres approved the study protocol. All patients provided written informed consent before randomisation. The authors were responsible for the design and analysis of the study and take full responsibility for the integrity and completeness of the data and the content of this article.

Participants

Patients aged 18 years and older who required elective DP, with or without splenectomy, performed either minimally invasive or through an open approach, for any indication were enrolled. The exclusion criteria included: pregnancy, DP performed as a secondary procedure during gastric or colonic resection, colonic resection required due to cancer extension, additional hepatic resection required, participation in another study that could interfere with the outcomes of this study, arterial resections other than the splenic vessels, or an American Society of Anaesthesiology physical status 4-5/WHO 3-4 (note: added

by amendment early in the course of the trial). To ensure sufficient surgical quality, participating centres had to perform at least 10 distal pancreatectomies (any diagnosis) annually and individual surgeons should have performed at least 50 pancreatic resections and 20 distal pancreatectomies (any type, any diagnosis) in the past 5 years prior to start of trial enrolment.

Randomisation

The randomisation was performed intraoperatively once metastases had been excluded and the decision had been made to proceed with the resection. The operating surgeon contacted the study coordinator via telephone to conduct the randomisation process. If it was decided to deviate from the assigned treatment during surgery, documentation and reason for this choice was required. All patients were centrally randomised in a 1:1 ratio to drainage or no drainage using an online computer-controlled permuted-block randomisation module (Castor EDC, CIWIT B.V., Amsterdam, the Netherlands). The block sizes varied randomly from 4 to 8 patients. Stratification was performed for patients at low or high risk of POPF, based on the DP Fistula Risk Score (D-FRS),[9] and annual centre volume (<40 or ≥ 40 distal pancreatectomies annually). The entire randomisation process, including block sizes, was concealed from all local investigators, except the trial coordinators. Numeric randomisation codes were assigned to patients, and only the principal investigator had access to them. The source data were digitally stored and will be kept by the project leader for 15 years after the inclusion of the last patient. Patients and caregivers were not blinded.

Procedures

Eligible patients for the study were screened with the use of standard procedures, including multiphase computed tomography (CT), and identified during an outpatient clinical visit in each individual participating centre. Baseline characteristics were collected by the trial

coordinator prior to randomisation. The required clinical data were collected after randomisation using standardised case report forms, and for Dutch centres through the Dutch Pancreatic Cancer Audit. The data were stored in a web-based data collection software (Castor EDC, CIWIT B.V., Amsterdam, the Netherlands).

The surgical technique used for DP has been previously described.[12,13] In short, transection of the pancreas was performed with one type of stapler (Ethicon, powered Echelon) using the progressive stepwise compression technique as described by Asbun.[14] Herein, closure of the stapler is halted when resistance to closure is first felt, maintaining compression for approximately 15 seconds. Subsequently, the stapler compression is continued and halted when meeting resistance again. These steps are repeated until complete closure is reached, without rotating the stapler. Co-interventions for pancreatic stump closures, preoperative endoscopic injections, and the use of somatostatin analogues were not advised, and were allowed only when used already routinely in all patients undergoing DP (i.e. in both groups).

In the drain group (control group), the abdominal drain was placed intraoperatively after randomisation. In case of splenectomy, the drain including the side holes was placed beyond the former splenic bed with the tip next to the pancreatic transection margin while avoiding direct contact with the artery or vein stumps. Drain amylase levels were measured on day 1, 3, and 5 postoperatively (if still admitted to the hospital) and the drain was removed on day 3 unless the drain amylase levels exceeded three times the upper limit of the institution's range of serum amylase[15] and when the fluid exceeded 200 ml in 24 hours. Postoperative care followed the enhanced recovery principles.[16]

Outcomes

The primary outcome was the rate of major morbidity, defined as Clavien-Dindo ≥3 complications.[17] The most relevant secondary outcome was grade B/C POPF.[15] Other predefined secondary outcomes included the occurrence of grade B/C pancreatic specific

complications according to the International Study Group for Pancreatic Surgery (ISGPS): delayed gastric emptying (DGE)[18] and post-pancreatectomy haemorrhage (PPH),[19] and also the need for conversion, reoperation, radiological/endoscopic reintervention, wound infection, blood transfusion, length of hospital stay, in-hospital/30-day mortality, 90-day mortality, and readmission within 30 days. Morbidity was assessed up to 90 days after surgery. The definitions of all outcomes are listed in the appendix. Primary and secondary outcomes were crosschecked against the definitions by a blinded adjudication committee before final analysis.

Statistical Analysis

The sample size for the primary outcome of major morbidity was calculated based on the following assumptions: a 2·5% one-sided significance level (α), 80% power (1−β), and a non-inferiority margin of 8% for major morbidity (percentage of patients not affected by postoperative major morbidity of 77% in the no-drain group and 70% in the drain group, based on the multicentre randomised LEOPARD trial[20], considering an expected majority of minimally invasive procedures). With this calculation, the minimum number of patients required was 272. Considering a potential dropout of 3% after randomisation, the total required sample size was 280 patients. The sample size for the most relevant secondary outcome of grade B/C POPF was calculated based on the following assumptions: a 2·5% one-sided significance level (α), 80% power (1−β), and a non-inferiority margin of 8% for grade B/C POPF (percentage of patients not affected by grade B/C POPF of 81% in the no-drain group and 75% in de drain group, based on the trial of van Buren et al.[5]), resulting in a sample size of 274 patients. Accounting for a 3% dropout rate, the total required sample size was 282 patients. The larger sample size of 282 patients was used to ensure sufficient statistical power to assess the non-inferiority of no prophylactic abdominal drainage compared to prophylactic abdominal drainage for

both the primary and secondary outcomes. All analyses were performed according to the intention-to-treat principles. An exploratory per-protocol analysis was performed only for the primary outcome. Multiple subgroup analyses were conducted which were not described in the original protocol. These included subgroup analyses in low, intermediate and high POPF risk groups (based on the D-FRS), and in several high-risk clinical scenarios, including low volume centres (those performing <15 distal pancreatectomies annually), patients with > 500 mL blood loss, ASA ≥3, BMI ≥ 30 kg/m^2, and extended resection.[21] The primary and most relevant secondary outcome are presented as the difference between the no-drain and drain groups with a corresponding two-sided 95% confidence interval (CI). The upper limit of the 95% CI was compared with the predefined 8% non-inferiority margin of the primary and most relevant secondary outcome to test the non-inferiority of no prophylactic abdominal drainage, with the corresponding $p_{non\text{-}inferiority}$ following Dunnett and Gent.[22] Categorical variables were compared with the Chi-square or Fisher's exact test, as appropriate, and expressed as proportions. Normally distributed continuous variables were compared with the independent samples t-test and values were expressed as means (standard deviations). Non-parametric distributed continuous variables were compared using the Mann-Whitney U test and values were expressed as medians (interquartile ranges). A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Orchard Road Armonk, New York, US) and R for Windows version 4.3.1.

Role of the Funding Source

The PANDORINA trial was an investigator-initiated trial supported by an unrestricted grant from Ethicon UK (Johnson & Johnson Medical Limited, Edinburgh, UK). This grant was used for the salary costs of the trial coordinators and to provide Ethicon staplers for the centres

participating in the trial. The funders had no role in the study design, data collection, data analysis, data interpretation, writing the manuscript or the submission process.

RESULTS

Between October 3, 2020 and April 28, 2023, a total of 376 patients with left-sided symptomatic benign, premalignant, and malignant pancreatic tumours were screened for eligibility after which 94 patients were excluded (80 patients preoperatively and 14 patients intraoperatively). Eventually, 282 patients were randomised and included in the intention-to-treat population; 138 patients to the no-drain group and 144 to the drain group. No patients were excluded after randomisation. The per-protocol population included 131 patients in the no-drain group and 144 patients in the drain group, after exclusion of seven patients in the no-drain group that intraoperatively received a drain. The inclusion flow chart is shown in Figure 1. There were no patients with missing data on the primary outcome.

Baseline characteristics and operative details were well balanced for both the intention-to-treat (Table 1 and Table 2) and the per-protocol population (Appendix). The three most common indications were pancreatic ductal adenocarcinoma, pancreatic neuroendocrine tumour, and non-invasive intraductal papillary mucinous neoplasm in both the no-drain (52 patients, 37·7%, 31 patients, 22·5%, 27 patients, 19·6%, respectively) and drain groups (43 patients, 29·9%, 34 patients 23·6%, 31 patients, 22·2%, respectively). Three POPF risk groups were identified based on the D-FRS, as shown in Table 1. In the no-drain group, these were 44 low-risk patients (31·9%), 61 intermediate-risk patients (44·2%), and 33 high-risk patients (23·9%). In the drain group, these were 37 patients (25·7%), 77 patients (53·5%), and 30 patients (20·8%), respectively. A minimally invasive DP was

performed in 100 patients (72·5%) in the no-drain group and 106 patients (73·6%) in de drain group (Table 2).

Primary and most relevant secondary outcome

In the intention-to-treat analysis, the primary outcome major morbidity occurred in 21 (15·2%) patients in the no-drain group and in 29 (20·1%) patients in the drain group (difference -4·9%, 95% CI -13·77 to 3·97), thus confirming non-inferiority of the no-drain approach ($p_{non\text{-}inferiority}$= 0·002) (Table 3).

In the per-protocol analysis, major morbidity occurred in 21 (16·0%) patients in the no-drain group and in 29 (20·1%) patients in the drain group (difference -4·1, 95% CI -13·17 to 4·97), again confirming the non-inferiority of the no-drain approach ($p_{non\text{-}inferiority}$= 0·004). The predefined most relevant secondary outcome grade B/C POPF, occurred in 16 (11·6%) patients in the no-drain group and in 39 (27·1%) patients in the drain group (difference -15·5%, 95% CI -24·51 to -6·49, $p_{non\text{-}inferiority}$ <0·001). Here, the limits of non-inferiority were exceeded and superiority of the no-drain approach was confirmed when testing for superiority ($p_{superiority}$ <0·001).

Other secondary outcomes

Postoperative outcomes are shown in Table 3. The rate of overall complications (combining minor and major morbidity) was lower in the no-drain group (46 patients, 33·3% vs 73 patients, 50·7%, p=0·003), as compared to the drain group. The rates of postoperative radiological and endoscopic interventions (14 patients, 10·1% vs 24 patients, 16·7%, p=0.109) and reoperations (6 patients, 4·4% vs 4 patients, 2·8%, p=0·476) were comparable. Reoperations were mainly performed due to the occurrence of grade B/C PPH in both groups. No differences were observed in grade B/C PPH (5 patients, 3·6% vs 7 patients, 4·9%, p=0·607), surgical site infection (3 patients, 2·2% vs 10 patients, 6·9%, p=0·056), intensive care unit admission (8 patients, 5·8% vs 4 patients, 2·8%, p=0·209), and readmission rate (21 patients,

15·2% vs 25 patients, 17·4%, p=0·626). The length of hospital stay was shorter in the no-drain group (median 6 days (IQR: 4 – 7) vs 6 days (IQR 5 – 8), p=0·026).

The rates of in-hospitality/30-day mortality (1 patient, 0·7% vs 0 patients, 0·0%, p=0·489) and 90-day mortality (3 patients, 2·2% vs 0 patients, 0·0%, p=0·116) were comparable between the no-drain and drain groups. Reasons of death in the no-drain group were sepsis and a watershed infarct leading to multiple organ failure and death at a second admission in an ASA 4 patient (day 23), euthanasia for metastasised disease (day 72), and respiratory insufficiency at a second admission (day 65), all described in detail in the appendix. In the latter two patients, the cause of death was not suspected to be related to the trial.

POPF risk-adjusted outcomes

In the low-risk POPF group, the rate of major morbidity was lower in the no-drain group (2 patients, 4·5% vs 7 patients, 18·9%, difference -14·4, 95% CI -28·42 to -0·38, p=0·040), as shown in Table 4. The rate of major morbidity did not differ significantly between the no-drain and drain groups in the intermediate- and high-risk POPF groups. In the low- and intermediate-risk POPF groups, the no-drain group had significantly lower rates of grade B/C POPF (1 patient, 2·3% vs 7 patients, 18·9%, difference -17·9, 95% CI -30·85 to -4·95, p=0·012 and 6 patients, 9·8% vs 19 patients, 24·7%, difference -14·8%, 95% CI -27·08 to -2·72, p=0·025, respectively), as shown in Table 4.

High-risk clinical scenarios

The outcomes of the no-drain and drain groups in low volume centres, patients with > 500 mL blood loss, ASA ≥3, BMI ≥ 30 kg/m2, and extended resection are shown in Table 5. In low volume centres, a lower rate of grade B/C POPF was observed in the no-drain group as compared to the drain group (5 patients, 11·6% vs 17 patients, 33·3%,

p=0·013). In all other subgroups, no significant differences were observed in the rate of major morbidity and grade B/C POPF between the no-drain and drain groups.

DISCUSSION

This international, multicentre, randomised controlled non-inferiority trial demonstrated the non-inferiority of a no-drain policy in patients after DP in terms of major morbidity (primary outcome) as compared to prophylactic abdominal drainage. Interestingly, a no-drain policy reduced the rate of grade B/C POPF (predefined most relevant secondary outcome) and hospital stay. Outcomes differed in the three risk groups for POPF. In low-risk patients, a no-drain policy reduced both the rate of major morbidity and POPF. In intermediate-risk patients, a no-drain policy reduced the rate of POPF. In high-risk patients, no differences were observed in these endpoints between the groups. Finally, in several high-risk clinical scenarios, no additional risk for a no-drain policy was identified.

One previous multicentre randomised trial performed in the United States and Canada found no differences in the rate of grade ≥3 complications (26% vs 29%, p=0·477) and grade B/C POPF (12% vs 18%, p=0·114), between a no-drain policy and routine drainage after DP, respectively.[5] In most centers and countries, however, this trial did not change clinical practice, and routine drainage remained standard practice. This lack of change may be explained by the fact no patient benefit was shown from omitting drainage. This is confirmed by the recent Brescia guidelines.[2] A recent meta-analysis which included this randomised trial, next to four retrospective studies, observed significantly lower rates of major morbidity, POPF, and readmission in the no-drain group. The authors concluded that prophylactic drain

placement should be reconsidered, and that a future randomised trial with POPF risk-adjusted analyses was indicated.[8] Consequently, our group recently developed the D-FRS, aiming to differentiate between patients at high and low risk of POPF.[9] In the current trial, the D-FRS was used to stratify patients according to their risk of POPF, aiming to ensure balanced groups and facilitate reliable subgroup analyses. Moreover, in contrast to previously published studies, a standardised stump closing technique was applied using the same surgical stapler in all participating centres.[14]

The present trial provides the highest level of evidence that a no-drain policy after DP is safe in terms of major morbidity. Moreover, a no-drain policy actually reduced the occurrence of grade B/C POPF in about 1 in 6 patients and shortened hospital stay. How is this positive impact of a no-drain policy explained? A fluid collection at the transection site commonly occurs after DP, probably because of some extent of leakage of pancreatic fluids. This isn't necessarily problematic, much like an peripancreatic sterile collection in pancreatic trauma and pancreatitis, as long as it remains non-infected and asymptomatic. Typically, such collections are self-limiting. However, when a drain is introduced (as in prophylactic abdominal drainage), this may actually facilitate the development of a POPF. Furthermore, this may also increase the risk of infection with skin flora. The results of this trial provide supporting evidence for this hypothesis.

This study has several limitations that should be considered. First, specific drain-related patient symptoms were not documented. This could have provided valuable insights into patient satisfaction. Second, standardized imaging was not conducted in patients in the no-drain group, which could have detected and quantified the extent by which asymptomatic collections occur. This was not done as this was a pragmatic trial and asymptomatic collections are treated conservatively. Third, this study does not provide a clear answer to the question for which patients it is recommended to leave a drain. In

patients with a high risk of postoperative bleeding (coagulation disorders or use of anticoagulation) or extended resections it cannot be ruled out that leaving a drain in place actually prevents major morbidity. Moreover, patients with ASA 4-5 and WHO 3-4 scores were excluded, so the trials' findings do not apply to this category of patients.

Major strengths of the study were the stratification based on POPF risk and the standardised technique for pancreatic transection using the same surgical stapler with the progressive stepwise compression technique in all patients.[12,14] This technique aims to reduce the risk of POPF, by preventing damage to the pancreatic parenchyma through stapling.[14] Finally, due to the intraoperative randomisation, the number of dropouts was minimised.

CONCLUSION

This international, multicentre randomised controlled trial provides strong evidence for the safety of a no-drain policy after DP in terms of major morbidity.

Notably, this policy reduces the risk of grade B/C POPF, shortens hospital stay and, in patients at low risk of POPF, prevents major morbidity. No safety risk of a no-drain policy was found in various clinical subgroups. These results are expected to be practice changing with a no-drain policy as the new standard approach in eligible patients undergoing DP.

DATA SHARING STATEMENT

Deidentified individual participant data collected in the PANDORINA trial can be made available upon request. Please contact the principal investigators (RS, CHJvE and MGB) who will review all requests. The PANDORINA investigators will be allowed to approve all research performed with the shared data**.**

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The authors acknowledge the work of prof. Claudio Bassi who passed away on July 11, 2023, 75 days after the inclusion of the last study patient. The authors acknowledge the input from prof. Horacio Asbun who showed us his technique of no-drain policy combined with the progressive stepwise compression technique for pancreatic transection.

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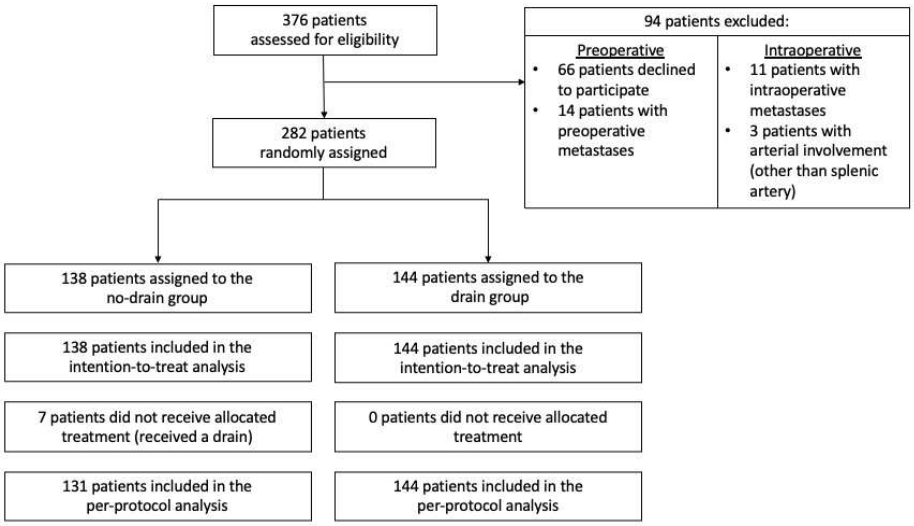
Figure 1. Inclusion flow chart.



TABLES

Table 1. Baseline characteristics of 282 patients after distal pancreatectomy in the intention-to-treat population

	No-drain group (n=138)	**Drain group (n=144)**	**p**
Female, n, (%)	75 (54.4)	73 (50.7)	0.539
Age, mean, (SD)	62.9 (12.5)	61.9 (15.5)	0.556
BMI, mean, (SD)	26.6 (4.5)	26.3 (4.4)	0.480
ASA score ≥ 3, n, (%)	42 (30.4)	34 (23.6)	0.197
Neoadjuvant treatment			0.951
Chemotherapy, n, (%)	12 (8.7)	13 (9.0)	
Chemoradiation, n, (%)	2 (1.4)	3 (2.1)	
Other, n, (%)	2 (1.4)	3 (2.1)	
Preoperative working diagnosis			0.734
PDAC, n, (%)	52 (37.7)	43 (29.9)	
pNET, n, (%)	31 (22.5)	34 (23.6)	
IPMN, n, (%)	27 (19.6)	32 (22.2)	
MCN, n, (%)	13 (9.4)	17 (11.8)	

SPN, n, (%)	2 (1.4)	6 (4.1)	
SCN, n, (%)	2 (1.4)	2 (1.4)	
Pancreatitis, n, (%)	6 (4.3)	3 (2.1)	
Other/unknown, n, (%)	5 (3.6)	7 (4.9)	
Tumour size, mm, median, (IQR)	28 (20 – 40)	28 (20 – 40)	0.452
Pancreatic duct diameter, mm, median, (IQR)	1 (1-3)	1 (1-2)	0.355
Pancreatic thickness, mm, median, (IQR)	12 (11-16)	12 (11-16)	0.215
POPF risk groups			0.290
Low-risk POPF (D-FRS <10%)	44 (31.9)	37 (25.7)	
Intermediate-risk POPF (D-FRS 10% – 25%)	61 (44.2)	77 (53.5)	
High-risk POPF (D-FRS > 25%)	33 (23.9)	30 (20.8)	

SD: standard deviation, BMI: body mass index in kg/m^2, ASA: American Society of Anaesthesiology, PDAC: pancreatic ductal adenocarcinoma, pNET: pancreatic neuroendocrine tumour, IPMN: intraductal papillary mucinous neoplasm, MCN: mucinous cystic neoplasm, SPN: solid-pseudopapillary neoplasm, SCN: serous cystic neoplasm, IQR: inter quartile range, D-FRS: Distal Pancreatectomy Fistula Risk Score

Table 2. Operative details in the intention-to-treat population

	No-drain group (n=138)	**Drain group (n=144)**	**p**
Type of approach			0.939
Robot-assisted, n, (%)	49 (35.5)	54 (37.5)	
Laparoscopic, n, (%)	51 (37.0)	52 (36.1)	
Open, n, (%)	38 (27.5)	38 (26.4)	
Conversion, n, (%)	2 (2.0)	3 (2.8)	0.528
Splenectomy, n, (%)	87 (63.0)	93 (64.6)	0.788
Operative time, min, median, (IQR)	194 (168 – 251)	215 (180 – 269)	0.054
Blood loss, mL, median, (IQR)	100 (50 – 250)	100 (50 – 300)	0.472
Staple time, sec, median, (IQR)	240 (180 – 240)	240 (180 – 240)	0.297
IQR: interquartile range			

Table 3. Postoperative outcome up to 90 days in the intention-to-treat population

	No-drain group (n=138)	**Drain group (n=144)**	**Risk difference (%) (95% CI)**	**p**
Complications Clavien-Dindo grade ≥ III, n, (%)	21 (15.2)	29 (20.1)	-4.9 (-13.77 to 3.97)	0.002 ($p_{non-inferiority}$)
Complications, all grades, n, (%)	46 (33.3)	73 (50.7)		0.003
Postoperative pancreatic fistula			-15.5 (-25.51 to -6.49)	<0.001 ($p_{non-inferiority}$) <0.001 ($p_{superiority}$)
Grade B, n, (%)	14 (10.1)	39 (27.1)		
Grade C, n, (%)	2 (1.5)	0 (0)		
Delayed gastric emptying				0.448
Grade B, n, (%)	1 (0.7)	5 (3.5)		
Grade C, n, (%)	1 (0.7)	0 (0)		
Postoperative pancreatic				0.607

haemorrhage				
Grade B, n, (%)	4 (2.9)	5 (3.5)		
Grade C, n, (%)	1 (0.7)	2 (1.4)		
Surgical site infection, n, (%)	3 (2.2)	10 (6.9)		0.056
ICU admission, n, (%)	8 (5.8)	4 (2.8)		0.209
Radiological /endoscopic reinterventio n, n, (%)	14 (10.1)	24 (16.7)		0.109
Reoperation, n, (%)	6 (4.4)	4 (2.8)		0.476
Length of stay, days, median, (IQR)	6 (4 – 7)	6 (5 – 8)		0.026
Readmission , n, (%)	21 (15.2)	25 (17.4)		0.626
CRP on day 3, mg/L, median, (IQR)	184 (131 – 244)	188 (138 – 258)		0.566
Days drain in, median, (IQR)	4 (3 – 5)	4 (3 – 15)		0.173
Tumour size on pathology	28 (20 – 43)	30 (19 – 48)		0.589

in mm, median, (IQR)				
In-hospital mortality, n, (%)	0	0		NA
30-day mortality, n, (%)	1 (0.7)	0 (0)		0.489
90-day mortality, n, (%)	3 (2.2)	0 (0)		0.116
ICU= intensive care unit, IQR= interquartile range, CI= confidence interval				

APPENDICES

Table of content

Definitions of outcomes

Conversion was defined as any incision other than trocar placement or specimen extraction. Length of hospital stay was defined as time between date of admission and date of discharge of initial admission. Overall complications were graded according to the Clavien-Dindo classification and pancreatic specific complications (POPF, DGE, and PPH) were graded according to the International Study Group for Pancreatic Surgery classifications.

Clavien-Dindo classification of surgical complications

Grades	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. This grade also includes blood transfusion and total parenteral nutrition.
III	Requiring surgical, endoscopic or radiological intervention. A: intervention not under general anaesthesia B: intervention under general anaesthesia
IV	Life-threatening complication (including central nerve system complications) requiring IC/ICU-management. A: single organ dysfunction (including dialysis) B: multi organ dysfunction

V	Death of patient

Reference: Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-13.

Postoperative pancreatic fistula (ISGPS definition)

Grade	**Definition**
Biochemical Leak	Amylase >3 times upper limit of the institutions' normal serum amylase value
Grade B	Persistent drainage >3 weeks after surgery* Clinically relevant change in management of POPF Percutaneous or endoscopic drainage* Angiographic procedures for bleeding* Signs of infection without organ failure*
Grade C	Surgical re-intervention required and/or IC/ICU management required and/or Death of patient

*Treatment/Event POPF related

Reference: Bassi C, Marchegiani G, Dervenis C, et al: The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery. 2017 March;161(3):584-591.

Delayed gastric empyting (ISGPS definition)

Time of onset: Early ≤ 24h Late > 24h	**Location:** Intraluminal: bleeding in gastrointestinal tract Extraluminal: bleeding outside gastrointestinal tract
Moderate bleeding: Drop Hb < 3 g/dL or 1.9 mmol/L Transfusion ≤ 3 PCs No further therapeutic intervention required No hemodynamic instability	**Heavy bleeding:** Drop Hb > 3 g/dL or 1.9 mmol/L Transfusion > 3 PCs Hemodynamic instability Therapeutic intervention required

Grade	**Time of onset, location and degree of bleeding**	**Clinical condition**	**Diagnostic consequences**	**Therapeutic consequences**
Grade A	Early, intra- or extraluminal, moderate	Good condition	Observation required, blood tests, ultra sound imaging, CT imaging	None
Grade B	Early, intra- or extraluminal, heavy OR Late, intra- or extraluminal, moderate	Most of the time in good condition, intermediary	Observation required, blood tests, ultra sound imaging, CT imaging, angiography, endoscopy	Transfusion required, MC/IC management required, endoscopic interventions, embolization, relaparotomy in case of

				early bleeding
Grade C	Late, intra- or extraluminal, heavy	Severely disrupted, life-threatening condition	CT imaging, angiography, endoscopy	Determine location of bleeding, angiography and embolization, endoscopy or relaparotomy, IC/ICU management
Reference: Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy haemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007 Jul;142(1):20-5.				

Appendix Table 1. Baseline characteristics of 275 patients after distal pancreatectomy in the per-protocol population

	No-drain group (n=131)	**Drain group (n=144)**	**p**
Female, n, (%)	73 (55.7)	73 (50.7)	0.404
Age, mean, (SD)	62.9 (12.7)	61.9 (15.5)	0.546
BMI, mean, (SD)	26.6 (4.5)	26.3 (4.4)	0.514
ASA score ≥ 3, n, (%)	40 (30.5)	34 (23.6)	0.196
Neoadjuvant treatment			0.970
Chemotherapy, n, (%)	12 (9.2)	13 (9.0)	
Chemoradiation, n, (%)	2 (1.5)	3 (2.1)	
Other, n, (%)	2 (1.5)	3 (2.1)	
Preoperative working diagnosis			0.645
PDAC, n, (%)	51 (38.9)	43 (29.9)	
pNET, n, (%)	29 (22.1)	34 (23.6)	
IPMN, n, (%)	25 (19.1)	32 (22.2)	
MCN, n, (%)	11 (8.4)	17 (11.8)	
SPN, n, (%)	2 (1.5)	6 (4.1)	
SCN, n, (%)	2 (1.5)	2 (1.4)	
Pancreatitis, n, (%)	6 (4.6)	3 (2.1)	
Other/unknown, n, (%)	5 (3.6)	7 (4.9)	
Tumour size, mm, median, (IQR)	28 (20 – 40)	28 (20 – 40)	0.401
Pancreatic duct diameter, mm, median, (IQR)	1 (1-3)	1 (1-2)	0.289

Pancreatic thickness, mm, median, (IQR)	12 (11-16)	12 (11-16)	0.135
POPF risk groups			0.189
Low-risk POPF (D-FRS <10%)	44 (33.6)	37 (25.7)	
Intermediate-risk POPF (D-FRS 10% – 25%)	56 (42.7)	77 (53.5)	
High-risk POPF (D-FRS > 25%)	31 (23.7)	30 (20.8)	
SD: standard deviation, BMI: body mass index in kg/m^2, ASA: American Society of Anaesthesiology, PDAC: pancreatic ductal adenocarcinoma, pNET: pancreatic neuroendocrine tumour, IPMN: intraductal papillary mucinous neoplasm, MCN: mucinous cystic neoplasm, SPN: solid-pseudopapillary neoplasm, SCN: serous cystic neoplasm, IQR: inter quartile range			

Appendix Table 2. Operative details in the per-protocol population

	No-drain group (n=131)	**Drain group (n=144)**	**p**
Type of approach			0.934
Robot-assisted, n, (%)	47 (35.9)	54 (37.5)	
Laparoscopic, n, (%)	47 (35.9)	52 (36.1)	
Open, n, (%)	37 (28.2)	38 (26.4)	
Conversion, n, (%)	2 (2.1)	3 (2.8)	0.557
Splenectomy, n, (%)	81 (61.8)	93 (64.6)	0.788
Operative time, min, median, (IQR)	191 (167 – 247)	215 (180 – 269)	0.020
Blood loss, mL, median, (IQR)	100 (50 – 265)	100 (50 – 300)	0.473
Staple time, sec, median, (IQR)	240 (185 – 240)	240 (180 – 240)	0.232
IQR: interquartile range			

Appendix Table 3. Postoperative outcome up to 90 days in the per-

	No-drain group (n=131)	**Drain group (n=144)**	**Risk difference (%) (95% CI)**	**p**
Complications Clavien-Dindo grade ≥ III, n, (%)	21 (16.0)	29 (20.1)	-4.1 (-13.17 to 4.97)	0.004 ($p_{non-inferiority}$)
Complications, all grades, n, (%)	44 (33.6)	73 (50.7)		0.004
Postoperative pancreatic fistula				0.001
grade B, n, (%)	13 (9.9)	39 (27.1)		
grade C, n, (%)	2 (1.5)	0 (0)		
Delayed gastric emptying				0.451
grade B, n, (%)	1 (0.8)	5 (3.5)		
grade C, n, (%)	1 (0.8)	0 (0)		
Postoperative pancreatic haemorrhage				0.672
grade B, n, (%)	4 (3.1)	5 (3.5)		
grade C, n, (%)	1 (0.8)	2 (1.4)		
Surgical site infection, n, (%)	3 (2.3)	10 (6.9)		0.069
ICU admission,	7 (5.3)	4 (2.8)		0.278

pn, (%)				
r Radiological/e ondoscopic t reintervention, on, (%)	14 (10.7)	24 (16.7)		0.151
cReoperation, n, o(%)	6 (4.6)	4 (2.8)		0.425
l Length of stay, days, median, p(IQR)	6 (4 – 7)	6 (5 – 8)		0.040
oReadmission, pn, (%)	21 (16.0)	25 (17.4)		0.768
uCRP on day 3, l mg/L, median, a(IQR)	186 (136 – 250)	188 (138 – 258)		0.773
t Days drain in	-	5 (3 – 15)		NA
i Tumour size on opathology in nmm, median, (IQR)	28 (20 – 43)	30 (19 – 48)		0.603
In-hospital mortality, n, (%)	0	0		NA
30-day mortality, n, (%)	1 (0.8)	0 (0)		0.476
90-day mortality, n, (%)	3 (2.3)	0 (0)		0.107
ICU= intensive care unit, IQR = interquartile range, CI= confidence interval				

Causes of death patients with 90-day mortality

Three (2.2%) patients died within 90 days in the no-drain group versus 0 patients in the drain group (p=0.116). The first patient, characterized by a poor preoperative condition with an ASA score of 4 and a high risk for POPF (D-FRS=0.43), underwent a laparoscopic DP with splenectomy for a pNET. On days 3 and 6 postoperatively, a CT scan was performed because of an elevated CRP and abdominal pain without signs of POPF but mild signs of congestive heart failure. On day 8, the patient was discharged in good clinical condition but readmitted on postoperative day 11 with perihepatic and peripancreatic fluid collections. The fluid collections were drained radiologically and the patient was discharged on postoperative day 14. One day later, the patient presented at the emergency department with acute dyspnoea and sepsis after vomiting. A watershed infarct with paresis of right arm and leg turned out to be the underlying problem secondarily to sepsis which led to multiple organ failure and death.

The second patient was operated for a PDAC, had a low risk for POPF (D-FRS 0.08), and had no postoperative morbidity. However, the pathology report revealed a T3N1M1 tumour (with peritoneal and gastric metastases). The patient ended up in a palliative setting with death within 90 days.

The third patient underwent an open DP for PDAC with an intermediate risk for POPF (D-FRS 0.10). The patient received two packed cells because of 2800 cc perioperative severe blood loss. Besides this, the patient had an uneventful hospital stay and could be discharged at postoperative day 8. On postoperative day 65, the patient was admitted to the emergency department because of respiratory insufficiency after aspiration. After two days of ICU admission, the patient died due to respiratory failure.