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REVIEW ARTICLE

To drain or not to drain: a cumulative meta-analysis of the use of routine abdominal drains after pancreatic resection

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Abstract

Background: To warrant the adoption or rejection of health care interventions in daily practice, it is important to establish the point at which the available evidence is considered sufficiently conclusive. This process must avoid bias resulting from multiple testing and take account of heterogeneity across studies. The present paper addresses the issue of whether the available evidence may be considered sufficiently conclusive to continue or discontinue the current practice of postoperative abdominal drainage after pancreatic resection.

Methods: A systematic review was conducted of randomized and non-randomized studies comparing outcomes after routine intra-abdominal drainage with those after no drainage after pancreatic resection. Studies were retrieved from the PubMed, Cochrane Central Trial Register and EMBASE databases and meta-analysed cumulatively, adjusting for multiple testing and heterogeneity using the iterated logarithm method.

Results: Three reports, describing, respectively, one randomized and two non-randomized studies with a comparative design, met the inclusion criteria predefined for primary studies reporting on drain management and complications after pancreatic resection. These studies included 89, 179 and 226 patients, respectively. The absolute differences in rates of postoperative complications in these studies were –6.4%, –9.5% and –6.3%, respectively, in favour of the no-drain groups. The cumulative risk difference in major complications, adjusted for multiple testing and heterogeneity, was –7.8%, with a 95% confidence interval of –20.2% to 4.7% ($P = 0.214$).

Conclusions: The routine use of abdominal drains after pancreatic resection may result in a higher risk for major complications, but the evidence is inconclusive.

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Introduction

For several decades, the routine use of postoperative abdominal drains has been standard practice in abdominal surgery. The main rationale for this practice is the prevention of fluid collections in the abdomen and the detection of postoperative bleeding or anastomotic leakage.[1] However, the routine use of postoperative drains in abdominal surgery can itself provoke complications. These include haemorrhage, inflammation, retrograde bacterial migration, drain occlusion or loss, pain, and loss of fluids and electrolytes.[2] All such complications may delay recovery and prolong hospital stay. The standard use of drains is also interfering with attempts to accelerate recovery through enhanced recovery after surgery (ERAS) programmes.[3,4] Therefore, it is no longer self-evident that the benefits of the routine

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use of postoperative drains after abdominal surgery outweigh the associated risks.

Pancreatic resection may represent a special case in this respect because a postoperative leakage of the pancreaticojejunostomy is generally considered to pose an extra risk to the patient's recovery and health as a result of the autolytic properties of pancreatic juices.[5] However, as long ago as 1992, Jeekel questioned the routine use of postoperative drainage after pancreatic resection.[6] Since then, several randomized and non-randomized studies have addressed the subject.

As evidence on the safety and effectiveness of health care interventions accrues over time, a crucially important challenge is to decide when the evidence that has amassed on the benefit or harm of an intervention is clinically and statistically sufficient to warrant its adoption or rejection in clinical practice. For this purpose, the method of cumulative meta-analysis has been developed.[7,8] In the present study, this method was used to assess whether there is currently sufficient evidence to omit postoperative drainage after pancreatic resection without undue complications.

Materials and methods

Literature search

A search of the PubMed, EMBASE and Cochrane Central Trial Register databases was performed to identify studies on routine peripancreatic drainage after pancreaticoduodenectomy (PD). Search terms included 'drainage', 'drain*', 'suction', 'pancreatectomy', 'pancreatic resection', 'pancreaticoduodenectomy', 'pancreat*', 'postoperative complications', 'complication*', 'fistula' and 'abscess'. The full search strategy is shown in Appendix S1 (online).

Study selection and data extraction

Eligible studies were assessed on predefined inclusion criteria. In order to be considered as eligible, studies were required to: (i) report primary data; (ii) include a study population consisting of patients with suspected or histologically proven pancreatic or periampullary malignancy; (iii) include a population of patients undergoing pancreatic resection, including PD or distal resection, and (iv) compare routine peripancreatic postoperative drainage with no drainage. To make optimal use of the available evidence, randomized as well as non-randomized studies, conducted prospectively as well as retrospectively, were included taking into account any heterogeneity in the analysis.

Two reviewers independently assessed all titles and abstracts for inclusion. Disagreements were resolved by discussion. Full texts of studies eligible for inclusion were retrieved. The following data were extracted from the included studies: study design; inclusion and exclusion criteria; population size; baseline characteristics; duration of follow-up; statistical analysis; details of surgery and postoperative care, and outcome data. The methodological quality of studies was assessed using the MINORS (*m*ethodological *i*ndex for *n*on-*r*andomized *s*tudies) score.[9] This score has been found to be a valid and reliable measure of the methodological quality of surgical trials and can be used for both randomized and non-randomized studies. It rates the appropriateness of enrolment of patients, endpoints and their mode of assessment, follow-up, control group, and statistical analysis, as well as comparability at baseline.

Cumulative meta-analysis

The primary outcome of this analysis was risk for major postoperative complications. Major complications were defined as postoperative complications severe enough to result in radiologic, endoscopic or surgical intervention. Secondary outcome parameters were mortality rate and hospital length of stay (LoS). When necessary, authors were contacted and asked to provide details on the definition of endpoints. Quantitative data were entered into a database using the statistical software package StatsDirect.[10] For each study included, a 2×2 table was constructed to show the number of events (major complications) and non-events in the treatment (drain) and control (no-drain) groups. Risk differences and associated cumulative Z-scores were calculated, both unadjusted and adjusted, using the iterated logarithm method described by Hu *et al.*[11] A random-effects model was used, with total variance consisting of within- and between-study variance. To control for type I error, an adjustment factor (λ) of 1.5 was used, as recommended by Hu *et al.*[11]

Results

Studies included and their characteristics

The search produced 206 hits in PubMed (1969 to August 2011). The 21 and 55 publications retrieved from the Cochrane Trial Register and EMBASE, respectively, did not identify further eligible studies (Fig. 1). Three studies including a total of 494 patients met the predefined selection criteria.[12–14] Characteristics of these studies are summarized in Table 1.

The study by Heslin *et al.*[14] was a retrospective review of records of patients who underwent PD, with only little variation in surgery, including Roux-en-Y reconstruction and pylorus-preserving procedures. Patients in the drain group routinely received peripancreatic closed suction drains postoperatively. A total of 38 patients were not given drains; in 51 patients, closed suction drains were placed at the end of the procedure. Over 80% of the patients included had malignant disease. On histologic diagnosis, adenocarcinoma was found to be most prevalent. Locations of the tumour were the pancreas head (74%), ampulla of Vater (13%), duodenum (5%) and distal common bile duct (10%). Major complications were defined as death, reoperation, significant pancreatic leak, fascial dehiscence, re-intubation, pneumonia and intra-abdominal abscess. Major complications occurred in 27% [95% confidence interval (CI) 16–42%] of the drain group and 21% (95% CI 10–37%) of the no-drain group. Mean LoS was 12 days in both groups. Outcome measures are summarized in Table 2.

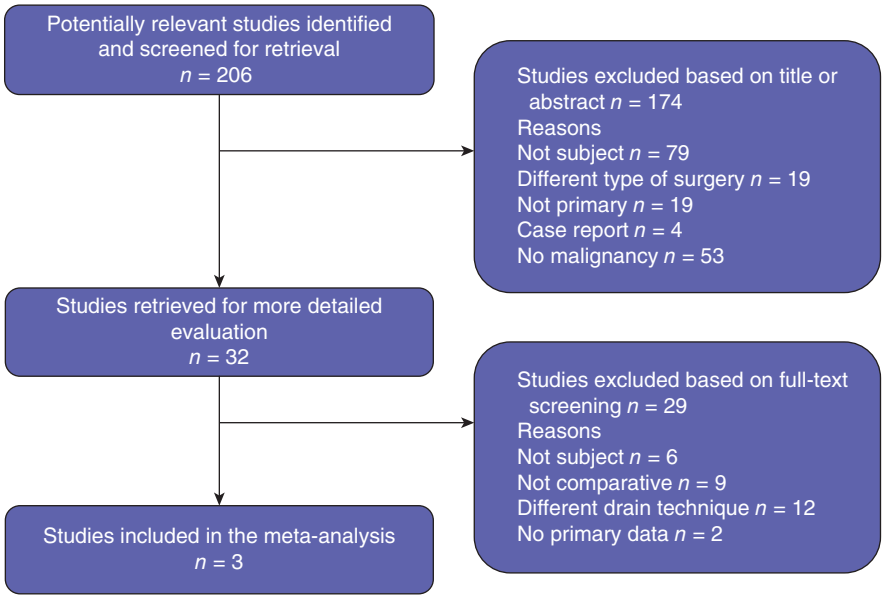

Figure 1 Flowchart showing the numbers of studies retrieved from the literature databases and the selection of studies according to inclusion and exclusion criteria

Table 1 Summary of key characteristics of the included studies

Characteristics	Heslin *et al*. 1998[14]	Conlon *et al*. 2001[12]	Fisher *et al*. 2011[13]
Country; time period when study was conducted	USA; 1994–1996	USA; time period when study was conducted not reported	USA; 2004–2009 (drain group) and 2009–2010 (no-drain group)
Design of study	Retrospective record review	Randomized controlled trial with two parallel groups	Prospective recording of data that were retrospectively reviewed
Patient population	PD for presumed or histologically proven periampullary malignancy	Adult, peripancreatic tumour, considered for surgical resection	Consecutive patients undergoing pancreatic resection
Type of surgery	PD/PPPD (n = 89)	PD (n = 133), PPPD (n = 6), DP (n = 40)	PD (n = 153), DP (n = 73)
Drain versus no drain, patients, n	51 versus 38	88 versus 91	179 versus 47
Follow-up period	Not reported	3 months	30 days
Primary and secondary endpoints	Postoperative complications; OR characteristics (duration of surgery, time in OR, blood loss, need for blood transfusion); pathology (presence of malignancy, presence of nodal metastasis, presence of positive margin)	Incidence of postoperative complications; mortality, re-intervention, hospital stay	Anastomotic failure, percutaneous abdominal drainage, delayed gastric emptying, infectious complications and organ failure, cardiovascular complications, length of stay, operative mortality.
Patient age, years, drain versus no-drain group	65 ± 2 versus 65 ± 2 (mean ± SEM)	69 (33–87) versus 66 (23–81) (median, range)	63 (53–72) versus 59 (51–70) (median, interquartile range)
MINORS score	12/24	16/24	15/24

PD, pancreaticoduodenetomy; PPPD, pylorus-preserving pancreaticoduodenetomy; DP, distal pancreatectomy; OR, operating room; SEM, standard error of the mean.

The study by Conlon *et al*.[12] was a randomized controlled trial (RCT). It included a total of 179 patients with peripancreatic tumours who were considered for surgical treatment and randomized to receive no drain (n = 91) or a closed suction drain (n = 88) placed at the end of the procedure. A total of 78% of the procedures were PDs and 22% were distal pancreatectomies (DPs). Because the authors did not classify the severity of complications, complications requiring interventional radiologic pro-

Table 2 Summary of outcomes of included studies. Numbers represent proportions and 95% confidence intervals, unless stated otherwise

Outcomes, no-drain versus drain	Heslin *et al*. 1998[14]	Conlon *et al*. 2001[12]	Fisher *et al*. 2011[13]
Operative mortality	Not reported	2% (0–8) versus 2% (0–8)	2% (0–11) versus 1% (0–3)
Major complications	21% (10–37) versus 27% (16–42)[a]	12% (6–21) versus 22% (14–32)[b]	15% (6–28) versus 21% (15–28)[c]
Minor complications	24% (11–40) versus 25% (14–40)	Not reported as separate category	11% (4–23) versus 8% (4–13)[d]
Fistula	3% (0–14) versus 6% (1–16)	0% (0–4) versus 17% (10–27)[e]	11% (4–23) versus 12% (7–17)[f]
Intra-abdominal abscess	0% (0–9) versus 6% (1–16)	7% (2–14) versus 7% (3–14)	4% (1–15) versus 6% (3–10)
Intra-abdominal collection	Not reported	2% (0–8) versus 7% (3–14)	Not reported
Reoperation	8% (2–21) versus 2% (0–10)	4% (1–11) versus 9% (4–17)	0% (0–8) versus 4% (2–9)
CT-guided drainage	3% (0–14) versus 4% (0–14)	8% (3–15) versus 13% (6–21)	11% (4–23) versus 2% (1–6)
Length of hospital stay, days	12 ± 1 versus 12 ± 1 (mean)	9 versus 9 (median)	7 (6–8) versus 7 (7–10) (median, quintiles)
Readmission	Not reported	Not reported	17% (8–31) versus 9% (6–15)

[a]Definition of major complication: death, reoperation, significant leak/fistula, fascial dehiscence, re-intubation, pneumonia, intra-abdominal abscess, myocardial infarction, pulmonary embolus, cerebrovascular accident, multisystem organ failure (Heslin MJ, personal communication, 2011).
[b]Complications requiring return to operating room or interventional radiology.
[c]Grade 3 or higher, Common Terminology Criteria for Adverse Events (CTCAE) classification.
[d]Grade 1 or 2, CTCAE classification.
[e]Includes enterocutaneous fistula and pancreatic fistula.
[f]Clinically significant, Grade B or C, International Study Group on Pancreatic Fistula classification.
CT, computed tomography.

Table 3 Difference in risk for major postoperative complications between patients with and without the routine placement of postoperative drains after pancreatic resection, using individual *Z*-statistics and cumulative *Z*-statistics, unadjusted and adjusted for multiple testing and heterogeneity across studies

Study	Risk difference, %	*Z*-statistic for each individual study	Cumulative *Z*-statistic, unadjusted	Cumulative *Z*-statistic adjusted (LIL-based) (random-effects model)
Heslin *et al*. 1998[14]	–6.4	–0.703	–0.703	–0.653
Conlon *et al*. 2001[12]	–9.5	–1.709	–1.889	–1.180
Fisher *et al*. 2011[13]	–6.3	–1.051	–2.128	–1.240

LIL, law of iterated logarithm.

cedures or a return to the operating room were rated as major complications. Such complications were reported in 22% (95% CI 14–32%) of patients in the drain group and 12% (95% CI 6–21%) of those in the no-drain group. Mortality within 30 days after surgery was 2% in both groups. Hospital LoS did not differ between the two groups; overall median LoS was 9 days (range: 5–11 days). Twenty-nine patients were readmitted to hospital. Of these readmissions, 19 occurred in the drain group and 10 in the no-drain group ($P = 0.07$). The median duration of readmission was significantly longer in the patients in the drain group (10 days versus 5 days; $P < 0.05$).

Fisher *et al*.[13] prospectively collected data for a total of 226 patients including 179 in whom postoperative drains were routinely placed after pancreatic resection (2004–2009) and 47 in whom no postoperative drains were placed after pancreatic resection (2009–2010). In this study, the Common Terminology Criteria for Adverse Events (CTCAE) index[15] was used to record complications; events of grade 3 or greater were considered as major complications. Major complications occurred in 21% (95% CI 15–28%) of patients in the drain group and 15% (95% CI 6–28%) of patients without drains ($P = 0.3$). No differences in median hospital stay (7 days) were observed between the two cohorts. The readmission rate was significantly higher in the no-drain cohort (17% versus 9%; $P = 0.007$). Of eight patients in the no-drain cohort who required readmission, five underwent percutaneous drainage for pancreatic fistula and the other three required observation only.

Cumulative meta-analysis

The results of the meta-analysis are presented in Table 3 and Figs 2 and 3. The proportions of patients with major postoperative complications were consistently lower in the no-drain groups compared with the drain groups. The differences in risk for major complications in the three studies[12–14] were –6.4% (95% CI –33.9% to 21.1%), –9.5% (95% CI –24.2% to 6.9%) and –6.3% (95% CI –20.2% to 4.7%), respectively. However, in none of the studies did this difference reach statistical significance. The unadjusted cumulative *Z*-score of the three studies[12–14] was –2.13, just

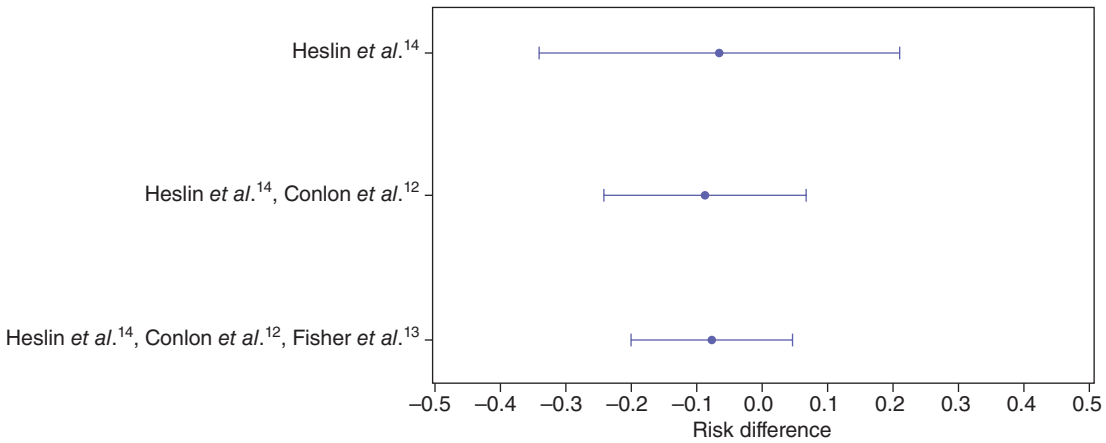

Figure 2 Cumulative random-effects meta-analysis using the law of iterated logarithm of three studies of routine postoperative drainage after pancreatic resection, showing risk differences and 95% confidence intervals

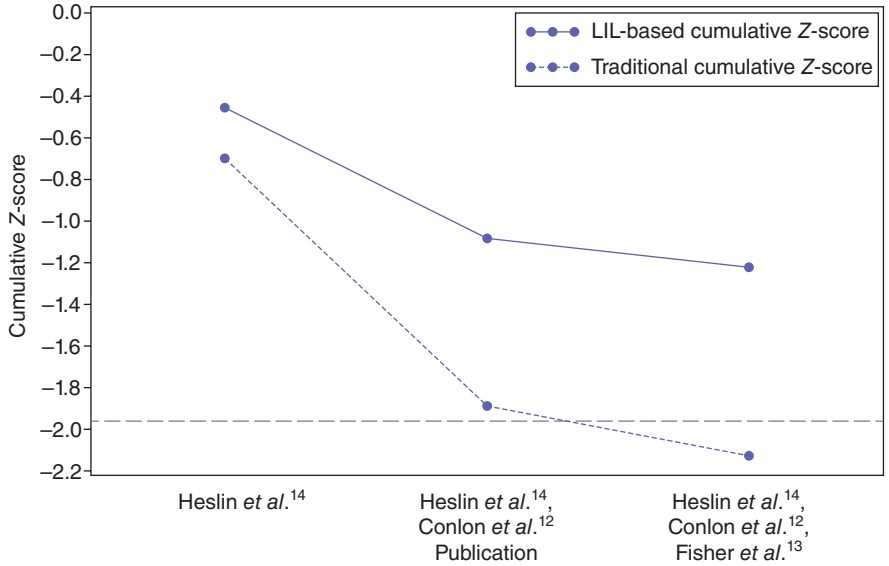

Figure 3 Cumulative meta-analysis of outcomes of routine postoperative drainage after pancreatic resection showing cumulative *Z*-statistics for the effect of omitting drainage on the occurrence of major postoperative complications. Traditional cumulative *Z*-statistics and *Z*-statistics are adjusted for multiple testing and heterogeneity. LIL, law of iterated logarithm

crossing the critical value of −1.96, which suggests that statistical significance was reached when the data from the study by Fisher *et al.*[13] were combined with the data from the previous two studies.[12,14] However, after adjustment for multiple testing and heterogeneity using the iterated logarithm method, the cumulative *Z*-score was −1.24, indicating that the difference had not reached statistical significance. The adjusted cumulative difference in risk for major complications for the three studies[12–14] was −7.8%, with a 95% CI of −20.2% (favouring no drainage) to 4.7% (favouring drainage).

Meta-analysis of the secondary endpoints (mortality and LoS) proved to be impossible because the requisite data on variance could not be extracted from the original studies[12–14] nor obtained from the authors.

Discussion

There is a persuasive logic to the practice of routine drainage after pancreatic surgery because drainage is assumed to allow for the early identification and monitoring of fluid collections and subsequently to prevent their negative impact on the patient's recovery. It seems, however, that the available evidence does not support this practice. In this study, a traditional meta-analysis of the available evidence pointed to a significantly lower complication rate in

the group without routine drainage. However, when a cumulative meta-analysis was performed with adjustment for repeated testing and heterogeneity, this difference was no longer statistically significant.

It is important to establish when the available evidence may be considered sufficiently conclusive to warrant the use of a particular intervention in daily practice. In this process, care should be taken to avoid bias resulting from multiple testing and heterogeneity across studies should be taken into account. Several methods have been developed to address this issue. Pogue and Yusuf[16] proposed the alpha-spending approach for controlling type I error in cumulative meta-analysis. However, this approach is a closed sequential process, requiring the pre-specification of the final sample size, which is usually unknown.[11] The approach used in this study was recently developed by Hu *et al.*[11]

The method proposed by Hu *et al.*[11] accounts for multiple testing and for heterogeneity across studies in a cumulative meta-analysis of trials with a binary endpoint. This method typically involves the performance of an updated meta-analysis every time that new evidence becomes available. Two challenges are encountered when using this method. Firstly, the procedure suffers from the problem of repeated testing and the associated inflated overall type I error (the unjustified acceptance of evidence of benefit or harm).[17] Secondly, because data may be pooled from studies that are spread over a prolonged period of time, medical technology, supportive care and patient populations may differ across studies, introducing substantial heterogeneity. The method, based on the law of *Z*-statistics, is an open and therefore more flexible approach towards controlling for type I error compared with those mentioned earlier. Moreover, it allows for reliable estimation of the between-study variance component, which is challenging, especially in a context in which the number of studies is small.[11]

In the studies[12–14] included in the present analysis, substantial heterogeneity was found. This related to research design, definitions of endpoints, patient populations, types of interventions and supportive care. In particular, the definition of what constitutes a major complication differed among the studies, none of which used a standardized scale such as the Clavien–Dindo system of classification. An attempt was made to pool the different results as adequately as possible by comparing the different scoring systems. Such heterogeneity is likely to represent the rule rather than the exception, and therefore should be taken into account in any analysis in which studies are combined to make optimal use of the available evidence.

With respect to postoperative drains, several studies on other types of surgery, such as colon and liver surgery, have shown that the use of abdominal drains is not beneficial in terms of postoperative outcome and may even be harmful.[18] Pancreaticoduodenectomy is technically one of the most challenging surgical procedures and is associated with potential anastomotic breakdown attributable to the activity of pancreatic enzymes; probably in response to this, surgeons tend to favour the conventional placement of abdominal drains. In order to avoid the risk for retrograde infection but to preserve the diagnostic safety drains are alleged to provide, some surgeons choose to place drains after every pancreatic resection and remove them after a short period of time. Kawai *et al.*[19] assessed 104 consecutive patients undergoing pancreatic head resection and came to the conclusion that removing the drain on postoperative day 4 rather than day 8 reduced the incidence of complications. A soft pancreas is thought to result in a higher incidence of complications and therefore Kawai *et al.*[19] also evaluated the impact of this clinical variable; however, the difference between groups in postoperative complication rates was not statistically significant. Bassi *et al.*[20] assessed 114 patients with a low prior probability of pancreatic fistula, including only patients with drain amylase levels of $\leq$5000 U/l. They concluded that the drain could safely be removed on postoperative day 3. Moreover, delayed removal of the drains (after postoperative day 5) led to a higher complication rate and increased hospital LoS and costs. Therefore, if abdominal drains are placed, it seems that their removal within a short period of time is justified.

It is important to note that two[12,14] of the three studies[12–14] included in this review included patients undergoing DP as well as those scheduled for PD among their study samples (113 of 494 patients, 22%). Heslin *et al.*[14] did not report the exact numbers of patients undergoing each type of resection. In the study by Conlon *et al.*[12] patients in the DP group were more likely to be allocated to the no-drain group than those in the PD group (DP group: drain group, $n = 15$ versus no-drain group, $n = 25$; PD group, drain group, $n = 73$ versus no-drain group, $n = 66$). In the study by Fisher *et al.*,[13] both PD and DP patients were equally divided between the drain and no-drain groups. Nonetheless, this potentially increases complication rates and makes adequate comparison more difficult because leak rates after DP have been reported to be 22%, whereas leak rates after PD have been reported to be 11%.[21,22]

The reluctance of surgeons to abandon abdominal drainage is understandable given the well-known detrimental effects of leakage of the pancreatojejunostomy and the absence of sufficiently powered, high-level evidence on prophylactic drainage after pancreatic resection. However, the development of less invasive radiologic intervention techniques benefits the treatment of postoperative complications such as intra-abdominal abscesses.[23] This may contribute to a reduction in surgeon anxiety in relation to the development of severe complications and eventually to the willingness to abandon abdominal drainage after pancreatic resection.

A recently published overview of the available evidence for the use of abdominal drains after pancreatic resection adopted a slightly different approach, using a standard Mantel–Haenszel random-effects model and separate evaluations of overall and specific complications, respectively.[24] It was concluded that more evidence is required before any firm conclusions on the use of abdominal drains can be reached, which is in line with the present findings. This overview[24] also included studies comparing the early and late removal of abdominal drains, which resulted in the inclusion of a higher number of studies. However, the study by Fisher

et al.[13] had not been published at the time this earlier analysis[24] was conducted and as a consequence its results were not included in the analysis. Moreover, Diener *et al*.[24] did not correct for heterogeneity and multiple testing and thus their results should be interpreted with great caution. Unfortunately, studies suitable for meta-analysis remain scarce and this affects the results of the present study to a similar extent as it has previous meta-analyses. Moreover, two of the studies[12,14] included in the present analysis were conducted at the same centre in different timeframes, which may have introduced bias to the present study. Nonetheless, both of these studies (randomized and non-randomized) were included in order to facilitate the pooling of data for as many patients as possible. In addition, in the current analysis, MINORS scores were used to rate the studies for quality. These scores provided evidence that the non-randomized studies included in the present analysis were of sufficient quality. It is of interest that the results of the non-randomized studies do not differ substantially from those of the RCT, which suggests that non-randomization did not introduce significant bias in the case of these two studies.

In conclusion, the current study shows the importance of taking into account multiple testing and heterogeneity within and between studies when conducting a meta-analysis. Without adjustment for the latter, the currently available evidence might be taken to imply that omitting drainage after pancreatic surgery leads to a statistically significant decrease in the risk for major complications. However, that conclusion is premature, as can be inferred from the present results when multiple testing and heterogeneity are taken into account. At present, an international, multicentre RCT intended to establish whether or not the prophylactic use of abdominal drains after PD can be abandoned is in preparation in the Netherlands. Until the results of such a trial become available, drain policy will depend on the surgeon's judgement. The available evidence suggests that it is reasonable to adopt a no-drain policy because not using a drain does not seem to increase postoperative complications.

Conflicts of interest

None declared.

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Supporting information

Additional supporting information may be found in the online version of this article.

Appendix S1. Literature search.