

## Peer Review File

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### **Reviewer A**

Thank you for this concise overview of the recent literature on two topics in pancreaticoduodenectomy (PD): intra-abdominal drains and nasogastric tube placement.

The conclusions and discussion with regard to NGT placement are clear. The advice should be to avoid routine NGT placement after PD.

The debate on intra-abdominal drains is quite complex. Although I support the carefully formulated conclusions I miss the cause and consequence discussion. Do drains really cause more morbidity or are more complications diagnosed with drains in situ? This question is a major bias in most retrospective studies and make firm conclusions and recommendations impossible. The second question that needs to be answered is the treatment of clinical relevant POPF. Does routine placement of a juxta-anastomotic drain lead to less post PD percutaneous or surgical drain placement? The latter has a big impact on the well-being and recovery of patients whilst an early removed drain has barely no morbidity. What is a reasonable number needed to treat to justify routine drain placement with an early removal protocol in case of low risk POPF. Furthermore, how many patients with clinical relevant POPF can be managed with a drain only and is this different between routine perop placed drains and drain on demand postop?

The manuscript could increase in relevance when the above questions are debated.

#### 1. In response to the comment of whether drains result in additional morbidity:

As you have pointed out, this a complex issue. I have reworded the section on drain placement so that it is less ambiguous. Three of the four included studies which report on the impact of drain placement (table 1) suggest perioperative mortality is lower in patients who undergo routine rather than selective drainage. The evidence is mostly from retrospective, non-randomised studies affected by bias. We suspect that this is partly as drains allow for the timely diagnosis and management of PPF/anastomotic leakage. However, we appreciate that this is an assumption and this finding may also reflect the fact that surgeons may elect not to place a drain in low-risk patients.

Two of the four included studies (table 1) suggest drain placement is associated with increased overall morbidity. With the data available, it is not possible to state whether

this is the result of drain placement or increased “pick-up” of certain complications such as POPF, bile leak or chyle leak. We suspect both are true to some degree. This has been made clearer. There is some evidence to suggest that the physical presence of drain and the resulting adjacent inflammation can contribute towards post-operative bleeding or disrupt anastomoses that they are placed near to. An indwelling line is also an infection risk (whilst at the same time reducing the risk of fluid accumulation and abscess formation). Furthermore, an indwelling line may limit patient mobilization and contribute to morbidity such as pulmonary embolism, atelectasis, ileus, pressure sores etc. Using the findings of the included studies, it is not possible to quantify these effects. Our take home message is that whilst drains may be associated with increased overall morbidity, they should be used routinely since they appear to correlate with reduced perioperative mortality. The manuscript has been adjusted to clarify this. As you have rightly mentioned, coming to firm conclusions is impossible but we feel our recommendation is reasonable based on the studies available.

2. In response to the comment on CR-POPF:

Two of the five included studies (table 1) suggest prophylactic drainage correlates with increased incidence of CR-POPF. Again, this is mostly based on the findings of retrospective, non-randomised studies and the other three studies did not observe this. It may be that surgeons elect to place a drain in high-risk patients. In addition, in some circumstances, the presence of a foreign body may hinder the newly-fashioned anastomosis. We have highlighted that this association was not observed in all studies and that the benefits of a drain likely outweigh the potential detrimental effects. We have suggested that a prospective, randomized study would be required to properly investigate this.

To investigate whether prophylactic drainage affects rate of re-operation or radiologic-guided drainage, we have gone back and looked at the included studies in detail. Interestingly, none of the studies show that the absence of a drain results in an increased likelihood of re-operation or radiologic-guided drainage. Again, this may reflect the fact that surgeons elect not to put drains in patients they deem low risk. This has been included in the discussion.

With regards to your query on number needed to treat, we have not speculated on this as we have advised prophylactic drain placement in all patients, even those deemed low-risk, since we feel the potential benefits outweigh the risks, particularly if the drain is removed in a timely manner. This has been made clear in the discussion. We have argued that all patients should have a drain and that all should be considered for early drain removal. However, we acknowledge that the criteria for drain removal, and what constitutes “early”, remain debated. We have suggested that further research

is required to get these answers (see updated discussion). We have advised that it is safe and reasonable to remove the drain on or before the third postoperative day providing day-one drain fluid amylase is <3 times the upper limit of the serum reference range (as per the ISGPS) and drain output is not excessive. We acknowledge that “excessive” is ambiguous and that this based on limited evidence (see updated discussion).

3. In response to the comment regarding the differences between a prophylactic drain and an on-demand drain:

We have updated the discussion to address this issue. We have advised a prophylactic drain in all patients. A prophylactic drain placed in theatre is not technically challenging and can be performed without the need for an additional procedure. It also comes with minimal risk and discomfort to the patient. An on-demand drain would require an additional procure. In addition, the patient would likely have POPF diagnosed at a later date and may suffer additional morbidity as a result of this. We acknowledge that this approach results in a proportion of patients receiving an unnecessary drain.

### **Reviewer B**

To consolidate the recent literature on drain and nasogastric tube use and their impact on perioperative outcomes of pancreatoduodenectomy (PD), the authors conducted narrative review and concluded that drain placement following PD improves perioperative mortality whilst increasing overall morbidity, and that the timing of drain removal, and the criteria for this, remain debated, and that nasogastric tubes should only be used in PD patients who require them clinically. This paper is well written; however, I have a following comment.

- (1) In tables 1, 2 and , each study should indicate the type of analysis such as MS, SR, and RCT.

The type of analysis has now been included in each table. An additional column has been inserted which outlines the study type (e.g. meta-analysis, single centre prospective) and the number of patients involved. We have also included odds ratios/risk ratios so that direct comparisons can be made.

### **Reviewer C**

The authors of this article attempted to review the current evidence regarding drain and nasogastric tube use after pancreaticoduodenectomy. However, as a reviewer, I think the authors failed to do that for the following reasons.

First, the essential requirement of a review is its accuracy, comprehensiveness, and fairness. This narrative review lacks the accuracy of the description of the results of each study.

As the findings of many studies have been included and multiple topics discussed, we did not go into great detail when describing each individual study. The manuscript has been re-written so that further detail is provided regarding the strengths and limitations of the included studies.

For example, on page 5, line 201, the authors described that ‘although interesting, these findings are of limited significance since PD patients are highly unlikely to meet these criteria in the early postoperative period.’ However, according to the cited article, about half of the patients who underwent PD fulfilled these criteria. Additionally, on page 5, line 207, the authors described that ‘again, this is of limited significance since few patients are likely to meet all of these.’ However, the cited article mentioned over 90% applicability of early drain removal criteria.

Based on the points mentioned above, this narrative review contains a fundamental inaccuracy in the description of the results of each study.

These comments were made as we felt, in our experience, very few patients who have undergone a major resection would be expected to have a CRP <14 on the third postoperative day. Hence, we felt that applying the findings of this study to our population would be of limited use. When looking at these studies for a second time we have realized that an error has been made on our part regarding units. We had interpreted the figures as mg/L (as our unit does) as opposed to mg/dL (in the study). We have updated the manuscript and apologize for this oversight.

Second, Table 1 only shows the increased or decreased risk (arrows) of each postoperative complication. Such an obscure description does not enable an adequate comparison between studies and significantly reduces the value of this review. The review should provide more detailed information on the results of each research or meta-analysis.

The tables were created to act as an easily readable quick reference which summarises what is outlined in the text. In their original format we appreciate that they lacked detail but we felt this was reasonable as exact figures for comparison were mentioned in the text and we did not want to overcrowd the tables. However, after taking your comments on board, we have provided additional columns such that they are more accurate and informative (with relative risk, hazard ratio or exact figures where available).

Third, this review lacks a PRISMA schema of reviewed studies. The PRISMA schema is a prerequisite of recent review articles to secure comprehensiveness and fairness.

Since we have aimed to cover four separate topics (routine vs selective drainage, the use of DFA, drain removal and NG tube use), rather than answer a specific research question, we have styled the article as a narrative review rather than a systematic review. We have done this as we aimed to provide a broad overview in a concise format. It is our understanding that a PRISMA checklist should be used for a formal systematic review. We have filled out a narrative review checklist as per the instructions on the journal website. We understand that is not as robust as a systematic review and it is more subject to bias. However, we have tried to include all relevant studies as per the methods section and have not deliberately omitted any studies.

Finally, this review is a superficial description of retrospective large-scale studies or meta-analyses in the current form. As a narrative review, the authors should discuss the shortcomings of each study in more detail and suggest the future direction of further research.

For example, most of the studies included in this review are retrospective. There is a considerable discrepancy in the background of groups with drain and without drain insertion after PD. The authors should discuss such problems adequately and suggest a solution like a propensity match analysis to minimize the background discrepancy.

The manuscript has been rewritten so that more detail is included on each study (including strengths and limitations). Furthermore, our opinion on what future research should focus on has now been included.

In the conclusion section, the authors stated that ‘a robust study is required to investigate this further.’ However, this sentence does not suggest any specific measures. The authors should mention their plan or suggestion in more detail.

We have removed this comment from the conclusion so that it does not come across as a “throw-away” comment. As mentioned previously, the discussion has been updated so that are opinions on what future research should focus on is covered in more detail.