Author’s response to reviews

Title: Comparison of different feeding regimes after pancreatoduodenectomy - a retrospective cohort analysis.

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Author’s response to reviews:

Reviewer #1: Guilbaud et al. present a retrospective analysis of three different feeding regimes after partial pancreaticoduodenectomy. The topic is worth of presenting it and the manuscript is well presented. However, I have some Major concerns which should be addressed prior to a possible publication:

Title: page 1

Please shorten the title and include the study type e.g. "Comparison of different feeding regimes after partial pancreatoduodenectomy - a retrospective cohort analysis"

Thank you for this comment. We have shortened the title according to your suggestion. The new title is as follows:

Title, line1; page 1:
“Comparison of different feeding regimes after pancreatoduodenectomy - a retrospective cohort analysis”

Abstract: page 2

Here it says that the aim was only to evaluate DGE. Please state clearly what was the main Goal of the study or just say, that you wanted to analyze the General outcome, which would be perfectly OK for an explorative study.

Thank you for this suggestion, in accordance to an explorative study the main goal of the study was to analyze the general outcome.

Abstract, line 5-6; page 2:

The aim of the study was to assess the safety and efficacy of nasogastric (NG), gastrostomy (GT), and gastrojejunostomy (GJ) tubes with different feeding systems on postoperative courses.

Please use the same conclusion here as in the manuscript text.

Thank you for this comment. In order to harmonize the conclusion, the same conclusion as in the manuscript text was used.

Abstract, line 17-19; page 2:

GT tube insertion with TPN was associated with increased severe postoperative morbidity and DGE and should not be recommended. EN through a GJ tube after PD is feasible but does not have clear advantages on postoperative courses compared to an NG tube.

Background: page 3-4

Here the primary endpoint is postoperative morbidity and mortality.

Please harmonize in the whole manuscript.

Thank you for this comment. In order to harmonize background and results, the primary endpoint was detailed and the manuscript text was modified in the same way.
The primary end point of our study was to compare different gastric decompression systems and feeding routes with an NG tube with TPN, a GT tube with TPN, and a GJT tube with EN after PD, with pancreaticogastrostomy in terms of postoperative mortality, overall morbidity and pancreatic specific complications (PSCs).

Methods, line 9-29; page 6:

Postoperative courses and follow-up

Postoperative mortality included all deaths occurring prior to hospital discharge or within 30 days of the surgery.

Postoperative morbidity included all complications following the surgery until discharge and/or readmission within 30 days and was graded based on the Clavien-Dindo classification system. Severe morbidity included all complications graded Clavien-Dindo 3/4. PSCs included postoperative pancreatic fistula (POPF), bile leak, postoperative hemorrhage, intra-abdominal abscess, and DGE. POPF was classified according to the International Study Group of Pancreatic Surgery (ISGPS) [35]. Bile leak was defined as a bilious drainage from drains or bile collection requiring drainage and postoperative bleeding as the requirement of transfusion or endoscopic or operative intervention. DGE was defined and classified based on the ISGPS [36]. Blood examinations and drain amylase/lipase fluid were conducted on POD 1, 3, 5, and 7. Octreotide was given to patients when POPF grades B/C were diagnosed. An oral diet was started on POD 1. Abdominal CT scans were done at the discretion of each surgeon (fevers, elevated white blood count, unexplained hemodynamic instability, gastric emptying, bleeding, and abdominal pain). Only DGE grades B and C was evaluated because all patients had a gastric decompression and as a consequence, all patients fulfill the grade A criteria. Duration of gastric decompression through the NG tube, GT tube, GJ tube, and oral intake were at the discretion of the surgical team. After the stomach was kept in charge, GJ tube and GT tube were left in place two or three more days, after tolerated and sufficient oral intake. All patients were discharged home without GJ tube or GT tube. The drain was removed depending on clinical factors and on the amylase concentration in the drain fluid.

Follow-up examinations were conducted a first time one month after discharge then every 6 months for the first 2 years and annually thereafter with clinical examination, biochemical and computed tomography (CT) scans. The patient follow-up was completed in September 2016.
- Results, line 7-9, page 10:

Postoperative mortality and overall morbidity

The mortality and overall morbidity rates were 6% (n = 5) and 73% (n = 63), respectively, including severe complications (Clavien-Dindo grade 3/4) in 55% of patients (n = 47, Table 4).

Methods: page 5-8

Please state clearly that, despite the prospective database, the study is retrospective as the decision which of the regimes was used was not part of the study.

Thank you for pointing this. We agreed with your suggestion.

Methods, line 4-5; page 5:

All patient data were obtained from a prospective database with an additional retrospective medical record review.

Furthermore, please make this point more clearly: Who decided which regime was used and by what criteria?

- Methods, line 15-19, page 5:

To achieve PD, either the duodenum (pylorus-preserving PD, PPPD) in one center or the antrum (pylorus-resecting PD, PRPD) in the other, was transected, followed by transection of the pancreatic neck, uncinate process, and jejunum distal to the ligament of Treitz. According to center preference, reconstruction was undertaken with a pancreaticogastrostomy, followed by an end-to-side choledochojejunostomy and either antecolic or retrocolic end-to-side duodenojejunostomy in patient with a PPPD or a gastrojejunostomy in patient with a PRPD.

- Methods, line 21-24, page 5:

At the end of the procedure, three different gastric decompression and feeding systems were used: a nasal NG tube with TPN (NG group) was inserted in patients with PRPD, and a GT tube plus TPN (GT group) or a GJ tube (MIC GJ-feeding tube, Halyard Health Inc., Alpharetta, GA, USA, GJ group) placement with EN was inserted in patients with PPPD.
The allocation of gastric decompression device was not randomized. GT tube was used between January 2013 and July 2015, and GJ tube was used from July 2015 to March 2016.

You distinguish PPPD from Whipple's procedure. Please state how much of the stomach was resected. If there is only few resected of the stomach you should better refer to the procedure as Longmire-Traverso or simply PRPD (Pylorus-resecting PD).

Thank you for this comment. We agreed with your suggestion and did modifications.

To achieve PD, either the duodenum (pylorus-preserving PD, PPPD) in one center or the antrum (pylorus-resecting PD, PRPD) in the other, was transected

Reference 35 is outdated; please cite the new one.

Thank you for pointing this. We have corrected these in the text and reference section

Please state at the beginning of the statistics paragraph that you only use descriptive statistics without an "a priori" hypothesis.

Thank you for pointing this. We have addressed this suggestion in the Methods section.
Methods, line 15; page 7: The Analysis used descriptive statistics without an “a priori” hypothesis.

Results: Page 9-12

The results are well presented and the complication rates are honestly reported and are in line with literature for medium size centers for pancreatic surgery.

Other than for POPF all grades of DGE are clinically relevant. The problem in this study may be that all patients fulfill the grade A criteria because they have a tube inserted on POD 7 at the discretion of the treating surgeon.

Please state this more clearly in the methods and discussion section, that you therefore only evaluate DGE B/C.

Thank you for this comment. We stated more clearly that we only evaluated DGE grades B/C.

Methods, line 21-22; page 6:

Only DGE grades B and C was evaluated because all patients had a gastric decompression and as a consequence, all patients fulfill the grade A criteria.

Please re-word: only biological POPF (grade A) to "biochemical leak"

Thank you for this suggestion.

Results, line 5; page 11:

biochemical leak (POPF grade A)

Discussion: page 13-15

Thank you for pointing this, indeed literature results are conflicting.

Discussion, line 23-29; page 13:


Page 14, line 54: Please also state that there are regimes using a combined enteral-parenteral nutritional Approach e.g. "Probst et al. Early combined parenteral and enteral nutrition for pancreaticoduodenectomy - Retrospective cohort analysis. Ann Med Surg (Lond). 2016 Feb 4;6:68-73."

Thank you for this suggestion, which has been added to the discussion.

Discussion, line 24-25; page 14:

The choice between enteral, parenteral nutrition or a combined enteral-parenteral nutritional approach after PD remains under debate[28-30,33,34] (Probst P, Keller D, Steimer J, Gmü J,

Please add to the conclusion that to answer your question, prospective and adequately powered study will be needed. Use this conclusion in the abstract.

Thank you for this comment.

Discussion, line 21-22; page 15:

Further analyses on larger and prospective series are warranted for confirming the robustness of these results.

Reviewer #2: Dr. Guilbaud and colleagues present a retrospective review of 86 patients who underwent pancreaticoduodenectomy in order to assess the efficacy of postoperative courses of nasogastric, gastrostomy and gastrojejunostomy tubes and feeding systems on delayed gastric emptying (DGE). The authors found that enteral nutrition through a GJ tube did not have the advantage of reducing DGE, hospital length of stay or cost savings. In addition, they found that gastrostomy tube insertion with TPN was associated with increased postoperative morbidity and DGE and should not be recommended. Overall, the paper is well-written; however, it has some significant limitations; most of which are acknowledged in the last paragraph of the discussion.

I have the following specific comments/questions:

1. Did the nutrition costs include the cost of enteral nutrition as well as the parenteral nutrition?

Thank you for your comment. However, our manuscript clearly pointed how cost of enteral nutrition as well as parenteral nutrition were measured:

- Methods, line 3-4; page 7:

“These costs were those associated with the following: length of hospital stay, EN or TPN cost and duration of the nutrition, intensive care unit length of stay, and the length of stay after 30-day readmission.”
“Daily costs for enteral and parenteral nutrition were obtained from the register of the pharmacy service.”

2. How long was the follow-up?

Thank you for pointing this. All patients were followed at least six month after discharge.

Follow-up examinations were conducted a first time one month after discharge then every 6 months for the first 2 years and annually thereafter with clinical examination, biochemical and computed tomography (CT) scans. The patient follow-up was completed in September 2016.

What were the costs associated with removal of the G and G-J tubes?

Thank you for the comment.

Gastric decompression devices management was clearly identified and did not need supplementary costs.

After the stomach was kept in charge, GJ tube and GT tube were left in place two or three more days until tolerated and sufficient oral intake and then they were removed.

Did any patient have a complication associated with tube removal (ie. Gastrocutaneous fistula requiring operative closure)?

Thank you for your comment. Our manuscript clearly pointed catheter-related complications and showed that parietal abscess occurred after removal of device in the GT group only, and that any catheter-related complications required reoperation.

Gastrocutaneous fistula did not occur in the GJ group or in the GT group, therefore this complication was not mentioned in our manuscript.
Results, line 13-16; page 10:

“The most common catheter-related complication in the GJ group was bowel blockage in 1 (8%) patient, followed by pain and parietal complication (abscess) after removal of gastrostomy in 4 (9%) patients in the GT group, whereas in the NG group in 4 (12.5%) patients, it was displacement. There were no catheter-related mortalities and no reoperation for a catheter- or feeding-related problem, even after removal.”

3. Patients in the G-tube and GJ-tube groups had an ASA score of 3 more often than those in the NG group and thus were sicker patients. Surgeon choice determined whether the patient received a G-tube or a GJ-tube. All patients in the NG group had a Whipple performed at a different center than those in the G-tube and GJ-tube groups who had a different operation, a PPPD, in a different center by (presumably) other surgeons. These three features of the study diminish the findings.

Our manuscript as well as your comment pointed these three features of the study.

Discussion, line 23-26; page 15:

“First, data were obtained within a multicenter study, and reconstruction was undertaken according to the surgeon’s preference. Second, this study is limited by the non-random allocation of patients to the different feeding tube techniques. According to the center preference, three different gastric decompression and feeding systems were used.”

4. With regard to the feeding protocol for the GJ group, did any patients go off protocol? If so, why?

Thank you for your comment.

Results, line 28-29; page 10:

Any patients get off protocol, therefore no patients needed nasogastric tube insertion or TPN in the GJ group.
5. What was the minimum amount of time the G-tube or GJ tube was left in? Typically, we leave these tubes in 1-2 months, so that the site can heal before we remove the tube. Is that your practice as well?

The mean duration of gastric decompression was 17 days +/- 12 in the GJ group, and 17 days +/- 13 in the GT group. Typically, gastric decompression devices in these two groups were left in place two or three more days, and where removed when oral intake was sufficient. All patients were discharged home without GJ tube or GT tube.

Methods, line 23-25; page 6:

After the stomach was kept in charge, GJ tube and GT tube were left in place two or three more days until tolerated and sufficient oral intake and then they were removed.

6. Why was nutrition not cheaper in the GJ group given the fact that they were on enteral feeds and needed less or no PN?

This item was pointed in the discussion of our manuscript.

Discussion, line 16-19; page 15:

“Although TPN is more expensive, the length of hospital stay in the group of patient with EN, largely offsets the price differential between TPN and EN.

Mean nutrition cost and mean global hospitalization cost were not decreased in the GJ group when compared to the NG group, and GT tube insertion with TPN nutritional protocol appeared as the most expensive for nutrition and hospitalization length of stay.”

7. There were more smokers in the GJ group than the NG group, p=0.05. If this is not accepted as significant, that is ok, but a borderline p-value like that should be addressed somewhere in the manuscript. This finding is similar to #3 above.

Thank you for this comment. Results associated with borderline p-value were added to the discussion.

Discussion, line 7-11; page 13:
However, the morbidity rate was 73%, including 55% severe morbidity (Clavien-Dindo grade 3/4), and tended to be higher in the GT and GJ groups in univariate analyses. These results could be explained by the fact that patients in these groups were smoker and had an ASA score of 3, more often than in the NG group and presented with more postoperative thromboembolic complications and respiratory and cardiac failures that required intensive care unit hospitalization.

8. In the discussion, the authors state that the G-tube and GJ-tube are kept in place longer, because the surgical teams are still reticent to apply tension to the gastrojejunal anastomosis and fear the consequences of a clinically relevant POPF. I believe there are two other factors involved here as well:

1) the patient complains more about the discomfort of the NG tube and wants it out,

Your highly relevant suggestion was stated in the discussion of our manuscript.

Discussion, line 4-8; page 14:

“Second, the disadvantages caused by gastric decompression devices are not the same. The GJ tube and GT tube are better accepted by patients than the NG tube, NG tube insertion has been associated with higher inconvenience for patients and can be dislodged. In addition, it may cause patient discomfort and is associated with nasal trauma, gastroenteral reflux, respiratory complications, and can lead to the dislodgement of the NG tube [23-26].”

2) the G-tube and GJ-tube tracts need to mature before they are removed; whereas, the NG can simply be pulled anytime.

Thank you for your comment, GT tube and GJ tube placement occurred at the end of the procedure and the stomach was fixed to the anterior abdominal wall. Therefore, GT tube and GJ tube tracts did not need a long time to mature before devices were removed. We clearly stated that in the Methods section.

Methods, line 24-25; page 5:

GT tube or GJ tube placement was followed by stomach fixation to the anterior abdominal wall.