

REVIEWERS' COMMENTS:

The authors would like to thank the reviewers the helpful comments they have made in order to improve the quality of the manuscript.

The new version of the article has been adapted meeting the requirements of the reviewers and focusing on the early complications derived from exocrine drainage of the pancreas and their management.

We hope that with the answers provided, the doubts of the manuscript have been clarified.

The responses to the three reviewers are detailed below:

REVIEWER #1:

SPECIFIC COMMENTS TO AUTHORS

This article discusses the enteric drainage techniques used in pancreas transplantation. It is structured more like a commentary rather than a scientific article.

1. The title is not appropriate. I recommend authors to get rid of the abdominal compartment section of the article, which doesn't have any novelty and subsequently change the article title as; Exocrine Drainage in Pancreas Transplantation: Complications and Management

In accordance with the reviewer, the article title has been changed to: "Exocrine Drainage in Pancreas Transplantation: Complications and Management".

2. The Abstract should be detailed as below, The aim of this study is to compare different exocrine drainage techniques used in pancreas transplantation. These techniques consist of bladder drainage and enteric drainage. Both techniques have different difficulties and complications. Methods The comparison between exocrine drainage techniques has been performed using reported complication and graft survival rates from the literature. Specific emphasis has been made on the early postoperative management of these complications and surgical infections.

In agreement with the comment, the abstract has been re-written, focusing on the reviewer's suggestions.

3. A conclusion specific to the pancreatic drainage techniques should be written. The conclusion comment of the article is too general, not novel.

The conclusion has been written as follows:

"Despite numerous techniques to minimize exocrine pancreatic drainage complications e.g leakage and infection, no universal technique has been standardized. A prospective study/registry analysis may resolve this."

4. Is chronic hematuria a different entity compared to late hematuria. If that is the case you should explain each in different paragraphs. • Early post-transplant hematuria • Late pos-transplant hematuria • Chronic microscopic hematuria Also, define what you mean by late? 6 months- one year?

As the manuscript is focused on immediate postoperative complications, and taking into account the length of the manuscript, the paragraph corresponding to late and chronic hematuria has been eliminated.

5. In the management of complications section, Depending on what conditions do you prefer repair over pancreatectomy?

The management of the early postoperative leak in the case of bladder-drained graft, is described as follows:

Treatment involves prolonged bladder decompression using Foley catheterization and percutaneous drainage of all intraabdominal fluid collections (early leaks). High-volume postoperative leaks or infected leaks in bladder-drained recipients with peritonitis require relaparotomy and surgical repair. A transplant pancreatectomy should be considered if there is significant compromise of the duodenal stump.

6. The article requires language editing.

We thank Steve Illing, *Cambridge RSA CELTA*, for English language assistance.

REVIEWER #2:

SPECIFIC COMMENTS TO AUTHORS

Review of early post-operative complications in pancreas transplantation with either bladder or enteric drainage.

- The title and abstract are confusing and not well-conceived.

In accordance with the reviewer, the article title has been changed to: "Exocrine Drainage in Pancreas Transplantation: Complications and Management".

Also the abstract has been rewritten.

- The conclusion is not necessarily supported by the data presented.

The conclusion has been rewritten as follows:

"Despite numerous techniques to minimize exocrine pancreatic drainage complications e.g leakage and infection, no universal technique has been standardized. A prospective study/registry analysis may resolve this."

- To my knowledge, abdominal compartment syndrome is a theoretical complication but it has not been specifically reported following pancreas transplantation.

In agreement with the comment, the text mentions the "Abdominal Compartment Syndrome (ACS) in pancreas transplantation" as it is a potential complication that must be taken into account in the context of intestinal leaks.

"Although there is a lack of reported cases in literature concerning **Abdominal Compartment Syndrome** (ACS) in pancreas transplantation, aspects of abdominal compartment mechanics have been depicted in some publications regarding liver transplant and HBP surgery^[77-79]. "

- None of the other information reviewed is particularly novel or illuminating.

All surgical innovations were described in relation with exocrine secretion drainage. The most relevant surgical novelties regard the use of duodenoduodenostomy for pancreas graft placement behind the right colon. Results of the larger series have been added.

- Bladder drainage has almost become of historical interest in pancreas transplantation.

Some immediate post-operative complications have been outlined in the text, taking into account the historical importance of BD in pancreas transplantation, and because it remains a preferred option at specific centres.

- The manuscript is not well-organized and is hard to follow at times. I didn't learn anything from reading this paper and I am not sure what the authors are trying to accomplish with this review because it is superficial and lacks detail or depth.

Because of the suggestion of the reviewer, some aspects have been analyzed more thoroughly and the text in general has been restructured.

REVIEWER #3:

SPECIFIC COMMENTS TO AUTHORS

Ferrer-Fabrega at el. described 6-immediate post-operative complications: digestive origin: Fistula. Urological origin in bladder drainage. Infection and collections. Abdominal compartment syndrome. Complications in pancreas transplantation.

- This is a nice review.

We thank the reviewer for the comment.

- The title is very confusing and there is no accent on the word pancreas.

According with the reviewer, the article title has been changed to: “Exocrine Drainage in Pancreas Transplantation: Complications and Management”.

- Could they describe those 6-immediate complications clearly?

Due to a typographical error, "6" referred to the section number, not the number of immediate complications.

- Could the authors describe in their papers what is new about pancreas transplant complications? Any correlations of immunosuppression drugs and pancreas transplant complications.

All surgical innovations were described in relation with exocrine secretion drainage. The most relevant surgical novelties regard the use of duodenoduodenostomy for pancreas graft placement behind the right colon. Results of the larger series have been added, including the management of enteric complications.

Immunosuppression with sirolimus is a risk factor for intraabdominal infections. However, complication rates have decreased due to the improvement in surgical techniques and the use of more potent immunosuppressive agents (i.e tacrolimus; resulting in lower rejection rates and less requirement for mono- or policlonal anti T – cell therapy).

- The authors only mentioned complications related to the type of pancreas

drainage (bladder or intestine). However, how about vascular complications.

Vascular complications are present in section 5 of the present manuscript. This is the reason why it is not mentioned here.

- In the methods the authors mentioned “The current prophylaxis schemes.....there is no descriptions of the current prophylaxis schemes.

Since each center has its own protocols, the phrase has been changed to: “Prophylaxis schemes (against bacterial, viral, and fungal infections), established from the moment of intervention by the transplants groups, have managed to reduce its incidence in the short term. “

- How the “low pancreas blood flow” increase the need for infection prophylaxis .

As the text has been restructured, this information has been eliminated to avoid confusion.

However, the low-flow state of the pancreas is a risk factor for graft thrombosis and a subsequently higher risk of intestinal leakage.

- Could the authors rewrite the conclusion? The conclusion is not clear.

The conclusion has been written as follows:

"Despite numerous techniques to minimize exocrine pancreatic drainage complications e.g leakage and infection, no universal technique has been standardized. A prospective study/registry analysis may resolve this."

- Why demanding and what is the meaning of “its high technical failure rate”?

Due to restructuring of the content, this sentence has been eliminated.

- Do the authors have the outcome of pancreas transplantation around the world?

As the present section is specific on “early pancreatic drainage complications”, outcomes of pancreas transplantation around the world have not been added.

Data from: OPTN/SRTR 2018 Annual Data Report: Pancreas. (Kandaswamy, et al. Am J Transplant . 2020;20 Suppl s1:131-192. doi: 10.1111/ajt.15673.) shows:

- The number of pancreas transplant recipients alive in 2018 (excluding re-cipients of multivisceral organs) increased to 18,800. Patient mortality at 1 year remained low for all pancreas transplant recipients, with rates of 3.0%, 1.5%, and 2.4% for PAK, PTA and

SPK, respectively. Five-year mortality for SPK continued to decrease to 8.1%, the lowest re-reported rate. Long-term mortality of 26.8%, 20.1%, and 25.3% at 10 years for PAK, PTA, and SPK, respectively, represent the cardiovascular comorbidity in this population. Five-year patient survival for all pancreas transplants in 2011-2013 performed in recipients with type 1 diabetes was 91.1%, compared with 95.2% in recipients with type 2 diabetes. In 2018, the overall rate of early loss was 5.9%, down from 8.7% in 2017, and the lowest reported rate in the past decade.

- Could the authors add the complication rate of superficial wound infections, intra-abdominal infections and abdominal compartment syndrome?

Superficial wound infections has been eliminated in order to focus on deep wound infections.

“As demonstrated, leaks remain a clinically significant entity, in particular as they are a risk factor for **intraabdominal abscesses**, of which up to 30% are associated with an anastomotic leak (duodenoenterostomy or duodenocystostomy) ^[21].”.

“Although there is a lack of reported cases in literature concerning **Abdominal Compartment Syndrome (ACS)** in pancreas transplantation, aspects of abdominal compartment mechanics have been depicted in some publications regarding liver transplant and HBP surgery^[77-79]. “)

- Did the authors compare pancreas transplants to intestinal, multivisceral, liver transplantation (adult and pediatric)?

No, we did not compare pancreas transplant to other abdominal transplants.