

January 19, 2016

Dear Editorial Board of World Journal of Gastroenterology,

Please accept our currently submitted manuscript entitled **“Total Pancreatectomy with Islet Cell Transplantation vs Intrathecal Narcotic Pump Infusion for pain control in chronic pancreatitis”** for consideration of re-review and publication as a Case Control Study. Intractable pain is the most common complaint in patients with chronic pancreatitis that can persist despite of multiple analgesic-based interventions. In this study, we compare pain control in chronic pancreatitis patients who underwent either total pancreatectomy with islet cell transplantation or intrathecal narcotic pump infusion. We found that pain control is comparable between the two interventions whereas the rate of insulin-dependent diabetes is still high few years after total pancreatectomy despite islet cell transplantation.

We appreciate all the suggestions and comments provided by our peer reviewers in order to clarify and our delivered message. Our detailed answers to the reviewers' comments are labeled in red below. We also made appropriate adjustments in the revised manuscript to address the points in question. Please refer to the “23815-Revised manuscript” document to follow these adjustments.

Reviewer #1 Comments: (Code 00039529)

Excellent study, particularly given the limitations of patient availability. Well written and analyzed. This is a potentially important message, and your follow-up should continue.

Answer to Reviewer #1:

We would like to thank reviewer #1 for his supporting comment and encouragement regarding our presented manuscript.

Reviewer #2 Comments: (Code 00043819)

Very interesting paper and topic. The main limitation is the retrospective nature of the study, the small number of patients enrolled in the ITNP Group, the short follow-up. Moreover, data were collected from different hospitals, so the indication for surgery or ITNP is not clear. Since ITNP was performed only in one Institute, it is difficult to compare results.

Answer to Reviewer #2:

We would like to thank reviewer #2 for his comments and concerns regarding the design of our study. We do agree that the number of patients with chronic pancreatitis who underwent ITNP is small to draw a solid conclusion. However, we were limited by the fact that this procedure is not offered as a routine “standard of care” option for pain control in these patients and the decision to try ITNP as an alternative to total pancreatectomy was left to the

patient after discussing with the treating physician the risks and benefits of both procedures overall. We clarified this decision by amending the MATERIALS AND METHODS section with the following sentences:

“All patients were managed at the discretion of their gastroenterology treating physicians at Indiana University and different approaches were selected based on clinical judgment and patient preferences. When patients’ final decision was to undergo ITNP, the procedure was arranged and performed at Indiana University Hospital. On the other hand, when patients decided to proceed with TP+ICT, the surgery was arranged to be performed in one of three different surgical centers that offer this procedure- including Indiana University Hospital- based on patients preferences and proximity to their.”

We also understand that comparison is sub-optimal when the interventions in question are performed in variable settings. We acknowledged this as one of the major limitations of our study and we amended the study limitation section of the CONCLUSION with the following statement:

“First, the study is retrospective as it will be difficult to prospectively design a large population study in patients with CP especially when it involves very extensive surgery like total pancreatectomy with islet cell transplantation which is only performed in few selected centers in the US. Second, the ITNP and surgical interventions were performed in different institutions which make comparison more difficult given the variability in technical performance. This discrepancy was due to the fact that ITNP was offered at Indiana University Hospital by the treating gastroenterologist there as a one day procedure like all other interventions provided. However, when the ultimate decision was to go for TP+ICT and since some patients came from out-of-state, the surgical center was chosen based on proximity to patients’ homes and social support. Third, not all surgical patients were assessed due to the fact that many surgeries were performed in multiple institutions and medical records were not available to us for review. In addition; three years median duration of follow up is still considered modest for CP. Larger comparative series with longer duration of follow up are needed to better characterize the optimal management of intractable pain in patients with chronic pancreatitis.”

Reviewer #3 Comments: (Code 00058446)

This is a retrospective study of Total Pancreatectomy (TP) + Islet Cell Transplantation (ICT) and Intrathecal Narcotic Pump infusion (ITNP) for the control of intractable pain in chronic pancreatitis (CP). The aim is to evaluate pain control in patients with CP from a single center. ITNP and TP+ICT are comparable for pain control in patients with CP, however with high incidence of DM among TP+ICT group. And prospective comparative studies and longer follow up are needed to define the treatment outcomes. 1. What is the indication for Total Pancreatectomy (TP) + Islet Cell Transplantation (ICT) or Intrathecal Narcotic Pump infusion (ITNP)? 2. Does the patient have high pancreatic duct pressure or pancreatic duct dilatation? 3. Does the patients need immunosuppressive therapy after TP +ICT?

Answer to Reviewer #3:

We would like to thank reviewer #3 for his comments and concerns regarding few unclarified statements in our study. We will answer them accordingly:

1. As detailed in the response for reviewer #2, the indication to undergo TP+ICT vs ITNP was made based on clinical judgment and patients preferences as the ITNP procedure cannot be offered as a routine stand of care option. We amended the section in the MATERIALS AND METHODS to better clarify this point. We also mentioned in the conclusion that randomized controlled prospective studies are needed in the future to truly evaluate the similarity of those procedures in pain control before recommending it on routine basis.
2. No. All patients with evidence of increased duct pressure were previously offered ERCP with sphincterotomy or surgical decompression like Puestow's procedure as detailed in table 2 before being considered for having a final total resection. We amended a new sentence in the MATERIALS AND METHODS to further clarify that point as follows:

"Patients with persistent evidence of increased duct pressure were offered decompression surgical or endoscopic decompression procedures- as appropriate- before being considered for total resection."
3. No. Patients with TP+ICT do not require any immunosuppressive therapy as the infused islet cells are their own. Thank you for drawing our attention to this point. We will add the word autologous to islet cell transplantation as appropriate in the text.

We hope that answers provided to the reviewers' comments address the concerns raised and the changes made to the manuscript accordingly will earn it final acceptance.

Sincerely,



Mohamad Mokadem, MD