Total pancreatectomy with islet cell transplantation vs intrathecal narcotic pump infusion for pain control in chronic pancreatitis

Mohamad Mokadem, Lama Noureddine, Thomas Howard, Lee McHenry, Stuart Sherman, Evan L Fogel, James L Watkins, Glen A Lehman

Mohamad Mokadem, Division of Gastroenterology and Hepatology, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa, IA 52242, United States

Lama Noureddine, Division of Nephrology and Hypertension, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa, IA 52242, United States

Thomas Howard, Community Health Network, Indianapolis, IN 46219, United States

Lee McHenry, Stuart Sherman, Evan L Fogel, James L Watkins, Glen A Lehman, Division of Gastroenterology and Hepatology, Indiana University Medical Center, Indianapolis, IN 46202, United States

Author contributions: Mokadem M and Lehman GA designed the study; Mokadem M, Noureddine L, Howard T, McHenry L, Sherman S, Fogel EL, Watkins JL and Lehman GA executed the experiments; Mokadem M and Lehman GL drafted manuscript; Mokadem M, Noureddine L, Howard T, McHenry L, Sherman S, Fogel EL, Watkins JL and Lehman GA critically revised the manuscript.

Institutional review board statement: All experiments were in compliance with the ethics of the Institutional Review Board of Indiana University Medical Center.

Informed consent statement: Oral informed consent was obtained from all patients before performing the questionnaire.

Conflict-of-interest statement: All authors declare no conflicts of interest.

Data sharing statement: All collected data is present within the core of the manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Mohamad Mokadem, MD, Division of Gastroenterology and Hepatology, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, 200 Hawkins Drive, 4570 JCP, Iowa, IA 52242, United States. mohamad-mokadem@uiowa.edu

Telephone: +1-319-3846178
Fax: +1-319-3547981

Received: December 18, 2015
Peer-review started: December 20, 2015
First decision: December 30, 2015
Revised: January 20, 2016
Accepted: February 20, 2016
Published online: April 28, 2016

Abstract

AIM: To evaluate pain control in chronic pancreatitis patients who underwent total pancreatectomy with islet cell transplantation or intrathecal narcotic pump infusion.

METHODS: We recognized 13 patients who underwent intrathecal narcotic pump (ITNP) infusion and 57 patients who underwent total pancreatectomy with autologous islet cell transplantation (TP + ICT) for chronic pancreatitis (CP) pain control between 1998 and 2008 at Indiana University Hospital. All patients had already failed multiple other modalities for pain control and the decision to proceed with either intervention was made at the discretion of the patients and their treating physicians.
Abdominal pain remains the most common and difficult to treat complaint for patients with chronic pancreatitis as it can often be severe and debilitating. There is still lack of full understanding of the exact mechanism of pain in chronic pancreatitis (CP) and factors contributing to it are only partially defined[1-3]. The general goals of treatment include pain relief in addition to prevention and management of disease related complications such as pseudocysts, strictures, malabsorption (exocrine failure) and diabetes mellitus (endocrine failure). Opiates, however, remain the most frequently used analgesics in the background of all other treatment options. It is the generally acceptable approach to start with the least invasive intervention first, such as alcohol and smoking abstinence, and then advance in a stepwise manner as the method fails[4-6]. Total pancreatectomy (TP) is considered the final resort offering additional pain control to most patients with remaining intractable pain at the expense of developing insulin dependent diabetes. The addition of autologous islet cell transplantation (ICT) to TP has been shown to have variable success in prevention of insulin dependence from zero up to a maximum of 40% based on the performing center and the duration of follow up[7-9]. Neuroaxial blockade modalities such as spinal cord stimulation or intrathecal analgesia are among the newer modalities that may have a role in CP. Experience in this field, however, has been limited to case reports[10-12]. Among these, the intrathecal narcotic pump infusion (ITNP) is the most studied modality for control of intractable pain in cancer as well as non-cancer patients but with variable level of success[13-16]. The ITNP consists of a channeled catheter intrathecally (into the subarachnoidal space) that is connected to a small battery-powered programmable pump which is placed in the subcutaneous tissue of the abdominal wall. In our institution, we used a Medronic Synchro MedII pump that possesses a 40 mL drug reservoir that is filled via a transcutaneous route under sterile conditions every 1-6 mo[17]. The literature has been scarce regarding its role and efficacy in patients with CP. In 2009, Kongkam et al[17] published a pilot study from the same center suggesting a promising role of ITNP in these patients.

MATERIALS AND METHODS

Using hospital electronic records and the endoscopic retrograde cholangiopancreatography (ERCP) database at Indiana University Medical Center from 1998 to 2008, we identified 13 patients who underwent ITNP infusion and 57 patients who underwent TP + ICT for CP and control of pain. The goal was to assess pain control in a cohort of surgical patients that is at least two fold the previously reported cohort of ITNP patients. 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 household. Patients with persistent evidence of increased duct pressure were offered surgical or endoscopic decompression procedures - as appropriate - before being considered for total resection. All patients available for follow up answered a phone call-based questionnaire inquiring about their pain level, their daily narcotic use and the number and duration of hospital admissions for pain control.

The phone call inquiry about pain control is part of the standard care provided by the gastroenterology group at Indiana University. Verbal informed consent was obtained from all patients before proceeding with the questions. The study design abides by the ethical guidelines of the “World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects”. Pain was assessed subjectively using a zero to ten scales (0 being no pain and 10 being maximum pain) before each procedure and on the last follow up available. All the daily narcotics used before and after the procedures were recorded and converted to milligram (mg) equivalent of oral morphine sulfate using a pharmacologic online converter http://www.globalrph.com/narcotic.cgi.

The number of in-hospital days per year for pain control was defined as the number of in-hospital admissions multiplied by the average duration of each admission (in days) divided by the total number of pain-years. This was recorded in each group before and after each intervention. Finally, the diabetes mellitus status, the average units of insulin used per day and the last HbA1C (glycosylated hemoglobin) were also recorded among the surgical group candidates on their last follow up.

### Statistical analysis

All data are presented as median or mean ± standard deviation. Only P-values that are less than 0.05 were considered statistically significant. Experiments comparing two means were analyzed using Student’s t-test with Welch’s correction if appropriate.

### RESULTS

The thirty patients who answered the phone call questionnaire constituted the surgery study group while no data was available from the remaining 27 surgical candidates. All 13 ITNP patients (5 male, 8 female) and the 30 TP + ICT patients (6 male, 24 female) contacted were Caucasians with a mean age of 40.6 years (± 9.6) and 39.9 years (± 14) respectively. The median duration of pain was 6 years (range 2-22) in the ITNP group and 7 years (range 1-21) in the TP + ICT group before each procedure. The median duration of follow up was 3 years in both groups with a range of 0.5 to 9 years in the ITNP group and 0.5 to 10 years in the TP + ICT group. The most common etiology of CP was idiopathic in the TP + ICT group (approximately 63%) followed by pancreatic divisum (approximately 17%), while it was pancreatic divisum (46%) followed by idiopathic in the ITNP group (approximately 23%). Alcohol constituted 15% of the ITNP group and approximately 7% of the surgery group (Table 1).

One ITNP patient developed serious meningitis requiring permanent removal of the catheter and pump and was excluded from the study. Three surgical patients were reported dead by their families upon contact, leaving 12 ITNP and 27 TP + ICT patients for retrospective comparison. All patients underwent multiple interventions for attempted pain control before either procedures such as ERCP with sphincterotomy (100% in both groups), celiac plexus neurolysis (46% of ITNP and 50% of TP + ICT), enteral tube feeding for bowel rest (61% of ITNP and approximately 33% of TP + ICT), and surgery (approximately 61% in ITNP and approximately 33% in TP + ICT).

The most common surgical procedure performed was denervation (bilateral splanchnicectomy) in the ITNP group and decompression (Puestow procedure) in the TP + ICT group (Table 2).

### Pain control

The pain score dropped from a mean of 8.1 (± 1.4) and a median of 8 before the ITNP to a mean of 2.5 (± 2.2) and a median of 2.5 on the last follow up (Figure 1A). Similarly, the pain score dropped from a mean of 8.0 (± 1.7) and a median of 8 before the TP+ICT to a mean of 2.7 (± 2.9) and a median of 2.5 on the last follow up (Figure 1B). No ITNP patients
reported increase in their pain score and 3 out of 12 were still pain free on their last follow up (duration of last follow up was 0.5, 5, and 9 years respectively). Two TP + ICT patients reported worsening of their pain after surgery and one reported no change. 12 surgical patients were still pain free on their last follow up with a median duration of 4 years. The daily narcotics usage among ITNP patients decreased from a median of 393 mg equivalent of morphine sulfate and a mean of 553 mg (± 448) before intervention to a median of 8 mg and a mean of 158 mg (± 349) on their last clinic follow up, respectively (P < 0.05) (Figure 2A).

Two ITNP patients had increase in their oral daily narcotic requirements, one patient had very minimal decrease in his dose and six were narcotic free on their last follow up. The duration of follow up ranged from 0.5 to 7 years with a median of 1.5 years. The average dose of intrathecal morphine was 7.5 mg (2-10 mg). Three TP + ICT had increase in their daily narcotic requirements and 9 patients were narcotic free on their last follow up. The duration of follow up ranged from 1 to 10 years with a median of 4 years. These same 9 patients also reported zero pain (Figure 2A and B).
units (range = 4-54 units). The last HbA1c reported by 25 units among the new diabetics with a median of 21 transplantation. The average insulin dose per day was on their last follow up despite the autologous islet cell surgical patients (approximately 15%) were insulin free intervention in both groups. Only 4 out of the 27 No patient had diabetes mellitus before either Complications (Figure 3A and B).

Hospital admissions
The number of in-hospital days per year (d/year) for pain control decreased from a mean of 22 d/year (± 34) and a median of 15 d/year before ITNP to a mean of 1 d/year (± 1.5) and a median of zero thereafter. Only one patient reported increase in his hospital admission days per year for pain control and 7 patients (64%) have not been admitted to the hospital for pain control as of their last follows up. Likewise, the number of hospital days dropped from a mean of 29 d/year (± 30) and a median of 15 d/year before total pancreatectomy to a mean of 8 d/year (± 2) and a median of zero on the last follow up. Two patients reported increase in their hospital admission days per year and 15 patients (55%) have not been admitted to the hospital for pain control as of their last follow up (Figure 3A and B).

Complications
No patient had diabetes mellitus before either intervention in both groups. Only 4 out of the 27 surgical patients (approximately 15%) were insulin free on their last follow up despite the autologous islet cell transplantation. The average insulin dose per day was 25 units among the new diabetics with a median of 21 units (range = 4-54 units). The last HbA1c reported by the TP + ICT patients had an average of 7.35% and a median of 6.6% (Table 3). There were 3 deaths in the TP + ICT group (10% mortality rate), 2 were due to sepsis occurring at 3 wk and 1 mo after surgery as reported by family. However, no further information was available for the third death case. One TP + ICT patient had abscess formation in the abdomen post-surgery requiring drainage. No other major surgical complications were reported by patients during the questionnaire; however, no surgical records were available for patients operated on at other institutions. No death to date occurred in our series among the ITNP group. Two out of the 13 patients who underwent the ITNP infusion had bacterial meningitis. One of them was serious enough to necessitate catheter and pump removal and was excluded from the study. One patient had CSF leak (7.7%) that was surgically repaired with no further reported complications.

DISCUSSION
Here we report two relatively similar series of patients with intractable pain due to chronic pancreatitis who underwent either an intrathecal narcotic pump infusion or total pancreatectomy with islet cell transplantation as a terminal procedure for pain control after failure of multiple other modalities. We considered two ITNP patients to have failed treatment because of higher narcotic use and increased hospital admission days upon their last follow up despite having lower pain scores.

Likewise, three TP + ICT patients can also be reported as failure due to worsening pain, higher narcotic use and increase in hospital admissions in 2 of them, and only higher narcotic use in the remaining one. Therefore, in our case series, success rate was observed as 77% (10/13) among the ITNP group and 80% (24/30) among the TP + ICT group for pain control. Most of the published case series reported a post-operative morbidity range (e.g. infections, anastomosis leak, etc.) between 25 and 68% but major complications constituted approximately 14%-18% based on their reporting. Several series from single centers reported a peri-operative mortality rate (usually defined as mortality within 2 wk of surgery) of 0% to 3.5% from total pancreatectomy. Our multi-center based data was incomplete as we were unable to record the morbidity and mortality among all 57 surgical patients. However, the thirty-day mortality, which may not reflect the exact peri-operative mortality, is found to be at best 3.5% (3 out of 57) and at worst 10% (3 out of 30). The rate of serious complications (like bacterial meningitis, CSF leak and pump or catheter migration) from intrathecal analgesia is not clear in the literature but reports vary from 0% to 20% depending on the center, the population studied, and duration of follow up. Anderson et al reported a success rate of 50% and 75% respectively using...
intra-thecal morphine in patients with chronic non-malignant pain after an average duration of follow up of approximately 2 years. This, however, drops to 30% and 44% respectively when success rate is defined as more than 50% reduction in visual pain scores.[14,16]. It is important to note that all our successful ITNP patients (10 out of 13) had more than 50% reduction in their pain scores with an average intra-thecal morphine dose of 7.5 mg/d (range 2.5-10 mg/d).

Our results from TP + ICT have been consistent with several previous series reporting successful pain control and narcotic independence in 70%-80% of subjects within 6-12 mo after surgery.[8,9,18,19]. Garcea et al.[20] reported in a series of 85 pts who underwent TP + ICT for CP that narcotic-free patients dropped from 90% after surgery to 40% at 1 year and ultimately to 16% at 5 years. On the other hand, Riediger et al.[21] reported 87% improvement in pain control of 224 patients as far as 10 years after pancreatic head resection. However, 72% of these patients were back on narcotic medications despite using lower doses. Therefore, the success rate of pain control after pancreactectomy seems to depend largely on the definition of “success”.[21]. Nonetheless, the most effective and most durable pancreatic surgeries performed for pain control in chronic pancreatitis seem to involve resection of the head of pancreas when compared with denervation or decompression procedures[16-21].

Our series had a 3 years median duration of follow up raising the question about the durability of the reported rate of 80%. The complete success of the autologous islet cell graft with resulting insulin independence has variably been reported to range from zero up to 40% within duration of follow up between 6 and 24 mo[8,9,18,19]. Garcea et al.[20] again showed in his series that insulin independence dropped from 14.1% post engraftment to 5.9% after a median follow up duration of 8 years. However, there still might be a role for ICT in diabetes management after TP since there is evidence of partial graft function in patients with insulin-dependent diabetes after pancreactectomy but with relatively low insulin requirements. Therefore, ICT may probably add some protection against hypoglycemia events and long-term diabetes complications. However, this need to be evaluated independently.[20,22]. Female gender, lower body weight and higher number of islet cells transplanted have been suggested to be positive predictive factors of graft survival[8,18,19]. Our data show a complete preservation of islet cells graft function in 15% of pts after a median follow up of 3 years (range 0.5-10 years) and an acceptable glucose control (average HbA1c 7.35%) with moderate insulin requirements (average 25 units/d) compared to patients with type 1 diabetes. Further follow-up of these patients is very important in order to assess for any further change in the islet cell graft viability and insulin requirements as in Garcea’s report.[20]. The incidence of diabetes mellitus complications awaits further follow up. Positive outcomes were very similar among both treatment modalities (Table 4) but major limitations still exist in our series.

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 such as total pancreactectomy with islet cell transplantation. The ITNP and surgical interventions were performed in only few selected centers in the United States. Second, the ITNP and surgical interventions were performed in different institutions which make comparison more difficult given the variability in technical performance.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Status of insulin-dependent diabetes among all surgical patients before and after total pancreatectomy with islet cell transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with insulin independence</td>
<td>Average dose of insulin/day (units)</td>
</tr>
<tr>
<td>Before TP + ICT</td>
<td>30/30 (100%)</td>
</tr>
<tr>
<td>After TP + ICT</td>
<td>4/27 (approximately 15%)</td>
</tr>
</tbody>
</table>

ITNP: Intrathecal narcotic pump; TP: Total pancreatectomy; ICT: Islet cell transplantation.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Summary of outcomes among patients with intrathecal narcotic pump and those with total pancreatectomy and islet cell transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITNP</td>
<td>TP + ICT</td>
</tr>
<tr>
<td>Reversibility of the procedure</td>
<td>Yes</td>
</tr>
<tr>
<td>Success rate for pain control</td>
<td>77%</td>
</tr>
<tr>
<td>Residual narcotic dose usage (mg equivalent of oral morphine sulfate)</td>
<td>Mean = 158 mg/d</td>
</tr>
<tr>
<td></td>
<td>Median = 8 mg/d</td>
</tr>
<tr>
<td>Percentage of patients with poor pain control</td>
<td>16.7%</td>
</tr>
<tr>
<td>Percentage of patients with new insulin dependent diabetes</td>
<td>0%</td>
</tr>
<tr>
<td>Procedure related death</td>
<td>0%</td>
</tr>
</tbody>
</table>

ITNP: Intrathecal narcotic pump; TP: Total pancreatectomy; ICT: Islet cell transplantation.
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.

In conclusion, our case series compared two advanced interventions offered to chronic pancreatitis patients who failed several conventional therapies and continued to have high reported levels of daily pain coupled with consumption of large dosages of narcotics. Total pancreatectomy is a morbid surgery associated with well-known short and long term peri-operative risks with insulin-dependent diabetes being one of its major sequela. Based on our data, the addition of islet cell transplantation to total pancreatectomy may offer a protective effect from insulin dependence at least for few years. This surgical procedure is not readily accessible to many patients within the United States or around the world.

On the other hand, intrathecal narcotic pump infusion is a relatively newer, less invasive therapeutic technique that delivers significantly lower doses of narcotics to the spinal fluid, therefore minimizing major systemic side effects of narcotics such as tolerance and constipation. There is very limited data of its long term efficacy and complications in chronic pancreatitis patients but observations can be extrapolated from reported patients with central nervous system disorders. Based on our data, ITNP seems to have a promising role as it showed comparable effect to total pancreatectomy on pain control with the additional benefit of preserving glucose and insulin metabolism. Future prospective studies in selected patients with chronic pancreatitis will better define its future role in pain management.

ACKNOWLEDGMENTS
We would like to thank all staff and personnel of the Division of Gastroenterology and Hepatology at Indiana University Medical Center who helped in the execution of this study.

REFERENCES


COMMENTS

Background
Chronic pancreatitis (CP) patients who still have intractable abdominal pain despite undergoing several endoscopic and surgical interventions for analgesia are left with very few options short of having a complete resection of their pancreas. Total pancreatectomy is associated with adverse effect of insulin-dependent diabetes which may be reversed or delayed by performing islet cell transplantation via infusion of isolated islet cells into the portal system. However, this surgery carries a significant risk of morbidity and mortality and is usually reserved as the last resort for pain control in chronic pancreatitis.

Research frontiers
Intrathecal narcotic pump infusion is a minimally invasive procedure aimed at delivering very low dose of narcotics to the spinal fluid through a small catheter for the purpose of analgesia with minimal narcotic’s side effects. This pump is currently used to manage severe pain in patients with refractory abdominal malignancies and in those with central nervous system injury and secondary spasms.

Innovations and breakthroughs
The authors examine - in a rare comparison - multiple markers of pain control in chronic pancreatitis patients who underwent either total pancreatectomy with islet cell transplantation or the less invasive yet relatively new procedure of intrathecal narcotic pump infusion.

Applications
The intrathecal narcotic pump (ITNP) infusion seems to have similar pain control to total pancreatectomy with islet cell transplantation (TP + ICT) with significant lower incidence of insulin-dependent diabetes. This modality may be considered as an option in chronic pancreatitis patients with intractable pain who refuse or do not qualify for total pancreatectomy.

Peer-review
This is a retrospective study of TP + ICT and ITNP for the control of intractable pain in CP. The aim is to evaluate pain control in patients with CP from a single center. Small series, but exceptionally well conducted, analyzed, and written. This is an important message that there may be a viable non-surgical alternative to TP and ICT for intractable pain in CP.


P- Reviewer: Bradley EL 3rd, Fu DL, Sperti C S- Editor: Gong ZM L- Editor: A E- Editor: Zhang DN