Total Pancreatectomy and Islet Autotransplant in the Treatment of Chronic Pancreatitis: Tread Very, Very Carefully

Timothy B. Gardner, MD, MS[1] and Kerrington D. Smith, MD[2]

Am J Gastroenterol advance online publication, 14 November 2017; doi:10.1038/ajg.2017.419

The severe abdominal pain symptoms of chronic pancreatitis are those most difficult to treat with current therapies (1). The increasing availability of and enthusiasm for total pancreatectomy with islet autotransplant (TPIAT) has led more centers to offer this intervention as a means of alleviating these chronic pancreatitis symptoms and improving quality of life (2,3). While many patients have improved from this surgery, our experience is that only very carefully selected patients—including a minority of patients with chronic pancreatitis—will derive enough benefit to offset the operative risks and lifelong complications that almost inevitably arise following TPIAT.

The most important factor to consider in offering TPIAT to a patient with chronic pancreatitis is whether or not the operation will relieve their pain (4). The trade-off to consider with TPIAT is the risk of lifelong diabetes, severe intestinal dysmotility, and/or the lack of significant pain relief versus the possibility of symptom improvement and a better quality of life. In essence, patients are often asked to "trade one disease (chronic pain) for another (diabetes and/or intestinal dysmotility)". Our experience at Dartmouth has been that patients on high dose opiates for an extended period of time without intervening periods of pain improvement (Ammann Type B pain), will not significantly benefit from TPIAT (5). In fact, it is these patients who are often seen for consultation in our pancreas clinic and also the patients (and their referring physicians!) who are generally most desperate for intervention. However, most chronic pancreatitis patients presenting for TPIAT evaluation, even when the diagnosis and degree of infirmity is not in doubt, should not be offered this surgery because the operation is unlikely to significantly improve their pain symptoms.

Although seemingly obvious, another critical issue is to make sure that patients undergoing TPIAT actually have chronic pancreatitis. Clinicians should be very weary about offering TPIAT to a patient with so called "minimal change" or "small duct" chronic pancreatitis in the absence of definitive morphologic and/or histologic evidence of disease. If the diagnosis is in doubt, it is imperative to err on the side of not offering TPIAT—isolated endoscopic ultrasound findings and/or subtle ductal abnormalities on MRCP or ERCP should not be used for definitive diagnosis. In some patients in whom the diagnosis is in doubt, we have resorted to laparoscopic pancreatic biopsy to prove or (mostly) disprove the diagnosis.

A multidisciplinary evaluation process is imperative for any center offering TPIAT. In addition to being evaluated by a medical pancreatologist, endocrinologist and pancreatic surgeon, in our opinion each patient should also be evaluated by a psychiatrist and pain management specialist. The primary role of the psychiatric evaluation is to make sure there are no mental health contraindications to surgery and additionally, to make sure the patient has the ability to cope with the severe stress inherent in the peri- and post-operative period. The pain management specialist's value is determining, to the best of their ability, if the TPIAT will relieve the patient's pain. At our multidisciplinary listing meetings, patients have been denied surgery solely based on the recommendation of the psychiatrist and/or pain management specialist.

An underreported consequence of TPIAT in our experience has been the development of severe intestinal dysmotility post-operatively, even in patients with no pre-operative motility disorder (6). Symptoms of bloating, intractable vomiting, and visceral pain are common in patients post-operatively, and in some cases can be just as debilitating as the pain from chronic pancreatitis. Until more is learned about the pathophysiology, natural history and treatment of this problem, patients need to be counseled about developing this condition, especially those with a pre-operative dysmotility disorder.

It is also critical for patients to understand that very little is known about the natural history of transplanted islet cells in the liver. For example, virtually no long-term outcome data greater than 10 years specifically addressing islet cell viability and the risk of diabetes is available. In addition, the malignancy risk of transplanted islets is not known. Furthermore, it is unclear if

[1]Section of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA; [2]Division of Surgical Oncology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA. **Correspondence:** Timothy B. Gardner, MD, MS, Section of Gastroenterology and Hepatology, Associate Professor of Medicine, Geisel School of Medicine at Dartmouth, One Medical Center Drive, Lebanon, New Hampshire 03756, USA. E-mail: timothy.b.gardner@hitchcock.org

This point-counterpoint seeks to explore both sides of a controversial topic in gastroenterology. The views presented here are not necessarily those of the authors.

Table 1. Factors which predict successful TPIAT in patients with chronic pancreatitis[a]

Characteristic	Optimal success	Less optimal success
Opiate use	No opiates	Longstanding opiates
Type of pancreatitis	Recurrent acute	Chronic
Pain Type	Ammann type A	Ammann type B
Etiology	Genetic	Idiopathic or toxic
Length of symptoms	<5 years	>10 years

[a]Opinion of the authors.

transplanted islets can eventually cause fibrosis in the recipient liver and lead to cirrhosis and its complications years after implantation. Clinicians should also remember that the decision to offer TPIAT must always primarily center on the likelihood of postoperative symptom relief—qualifying the risk of diabetes is a secondary consideration once it is decided that pain and quality of life will improve following pancreatectomy.

Despite our concerns, TPIAT can be an incredibly life-improving procedure for certain highly selected patients with chronic pancreatitis. While an NIH consortium trial led by the University of Minnesota is ongoing to try and definitively determine which patients will most benefit from TPIAT, we believe there are several factors which predict success. Younger patients who have not had clinical pain symptoms for greater than 5 years appear to benefit, as do patients who are not taking daily opiates at the time of surgery. Those with waxing and waning pain symptoms, so-called Ammann Type A pain, improve more often than do patients with chronic unrelenting (Ammann Type B) pain. In our experience, patients with hereditary pancreatitis (CFTR, SPINK1 and/or PRSS1), as opposed to other etiologies, also more often benefit (7). It is also important to differentiate between patients with chronic and idiopathic recurrent acute pancreatitis because severely debilitated patients with idiopathic recurrent acute pancreatitis benefit tremendously from TPIAT (8) (**Table 1**).

The ultimate challenge therefore for the clinician is deciding "if" and "when" to offer TPIAT to a debilitated patient with chronic pancreatitis. Unfortunately, most patients with chronic pancreatitis will not benefit from TPIAT and an ill-conceived surgery resulting in no or limited pain symptom improvement, diabetes and intestinal dysmotility is devastating. Denying TPIAT to a severely debilitated chronic pancreatitis patient and their loved ones is emotionally very difficult, but as clinicians faced with this decision we must be guided by our oath to *Primum non nocere* (first, do no harm).

CONFLICT OF INTEREST

Guarantor of the article: Timothy Gardner, MD, MS.
Specific author contributions: Both Timothy Gardner and Kerrington Smith contributed to the article.
Financial support: None.
Potential competing interests: The authors declare no conflict of interest.

REFERENCES

1. Forsmark CE. Management of chronic pancreatitis. Gastroenterology 2013;144:1282–91.
2. Kesseli SJ, Smith KA, Gardner TB. Total pancreatectomy with islet autologous transplantation: the cure for chronic pancreatitis? Clin Transl Gastroenterol 2015;6:e73.
3. Sutherland DE, Radosevich DM, Bellin MD *et al.* Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg 2012;214:409–24.
4. Walsh R, Saavedra JA, Lentz G *et al.* Improved quality of life following total pancreatectomy and auto-islet transplantation for chronic pancreatitis. J Gastrointestinal Surg 2012;16:1469–77.
5. Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. Gastroenterology 1999;116:1132–40.
6. John GK, Singh VK, Moran RA *et al.* Chronic gastrointestinal dysmotility and pain following total pancreatectomy with islet autotransplantation for chronic pancreatitis. J Gastrointest Surg 2017;21:622–7.
7. Dunderdale J, McAuliffe JC, McNeal SF *et al.* Should pancreatectomy with islet cell autotransplantation in patients with chronic alcoholic pancreatitis be abandoned? J Am Coll Surg 2013;216:591–6.
8. Bellin MD, Kerdsirichairat T, Beilman GJ *et al.* Total pancreatectomy with islet autotransplantation improves quality of life in patients with refractory recurrent acute pancreatitis. Clin Gastroenterol Hepatol 2016;14:1317–23.