

Total Pancreatectomy-Autologous Islet Cell Transplantation (TP-AIT) For Chronic Pancreatitis – What Defines Success?

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ABSTRACT

Chronic pancreatitis is an inflammatory disease which is characterized by irreversible morphologic changes that typically causes pain and permanent loss of the functions. The lack of good treatment options for patients with chronic pancreatitis is in part related to any therapy needing to address the “3Ps” that are necessary for this disorder. 1) Pain relief, 2) Prevention of brittle diabetes mellitus and 3) Prevention of pancreatic cancer. Total pancreatectomy and autologous islet cell transplant (TP-AIT) does offer a definitive therapy while addressing these three; however there has not been a universal uptake of this treatment to consider it the standard of care due to it being considered highly invasive and success being measured mainly by the concept of the length of insulin independence. However diabetes is an endpoint of chronic pancreatitis and this procedure offers the possibility of glycemic control albeit with some insulin use and therefore offers the best alternative to a life of pain, diabetes and cancer.

Keywords: Chronic pancreatitis, Autologous islet cell transplantation, Quality of life, Diabetes mellitus, Pancreatic cancer, Pancreatic surgery, Islet cell.

INTRODUCTION

Chronic pancreatitis is an inflammatory disease which is characterized by irreversible morphological changes that causes permanent loss of function. The incidence of chronic pancreatitis is 1.6 to 23 per 100,000 of the population and the prevalence is 10 to

30 per 100,000 in United States according to the National Institutes of Diabetes, Digestive and Kidney diseases (<http://www.niddk.nih.gov>). Patients with chronic pancreatitis suffer from debilitating pain, which progresses to significant narcotic medication requirement and deterioration in quality of life. Patients can undergo multiple endoscopic and surgical intervention procedures without significant success. In one report, pain recurs in over 50 percent of patients after having endoscopic surgical procedures¹. Total pancreatectomy may ameliorate the pain of chronic pancreatitis however the resultant severe brittle diabetes makes this a less than desirable option. Autologous islet cell transplant after total pancreatectomy (TP-AIT) gives patients with chronic pancreatitis the hope of pain relief and reduces the potential for brittle diabetes. There are multiple reports of TP-AIT being done with an emphasis on insulin independence at 1 and 2 years or 5 years and also the mean time of insulin independence as definition of success²⁻¹⁶. Possibly due to reports of insulin independence not being a universal outcome this procedure has received certain criticism being too drastic a procedure¹⁷. In this review we examine the value of this approach and why it may be hindrance to the management of these patients.

BACKGROUND

Patients with chronic pancreatitis typically seek medical help for abdominal pain. The pain eventually becomes intractable with patients not being adequately treated even with large doses of narcotics. Patients usually do not appreciate other complications that result from the chronic damage of the pancreas until a much later stage. The most striking of

these is the development of diabetes mellitus (type 3) due to destruction of the islet cells. Patients do however notice exocrine pancreatic insufficiency though symptoms may be obscured by the use of narcotics. Apart from pancreatic (endocrine and exocrine) dysfunction patients the third most important issue is the potential development of pancreatic cancer in someone with chronic pancreatic inflammation.

TREATMENT OPTIONS FOR CHRONIC PANCREATITIS

Most gastroenterologists would agree that treating patients with chronic pancreatitis is not a rewarding proposition. In the few patients that have a pancreatic duct or sphincter disorder endoscopic therapy may be of use however in reality most patients with chronic pancreatitis have multiple procedures with the futile hope that there is an unrecognized mechanical problem in the pancreatic duct that will be amenable to yet another procedure¹⁸. Non-endoscopic practices have been mainly aimed at methods to relieve pain the most scientific of which has been the use of pancreatic enzymes. As we have previously noted there is theoretical basis for the use of antioxidant regimens¹⁹. In practice the results have been mixed. The conservative surgical therapies like Puestow's procedure and Frey's procedure have some benefit^{20,21} however significant numbers of these patients have persistent pain and continuation of endocrine function damage and cancer risk²².

The lack of good treatment options for patients with chronic pancreatitis in part is related to any therapy needing to address the, "3Ps" that are necessary for this disorder.

"Pain relief" is a paramount and can mean the difference between a functioning employable person and one requiring constant care themselves.

"Prevention of brittle diabetes mellitus". Diabetes occurs from the disease itself and after removal of the pancreas to address the pain. The absence of islet cells not only results in a lack of insulin but also glucagon which may result in life threatening hypoglycemic events and brittle diabetes. Of course exocrine dysfunction by contrast is relatively easily addressed by enzyme therapy or with the use of predigested nutrition.

"Prevention of Pancreatic cancer" is the least well appreciated of the potential complication of chronic pancreatitis and little data exist on mechanisms involved. Nevertheless over time a chronically inflamed pancreas will clearly be at risk of this fatal complication.

TOTAL PANCREATECTOMY AND AUTO ISLET CELL TRANSPLANT AS A TREATMENT OPTION

A procedure originally pioneered by David Sutherland at the University of Minnesota, TP-AIT does offer a definitive therapy for chronic pancreatitis while addressing our "3Ps"^{23,24}. Although it can be taken for granted that pain relief will be the main initial objective the preservation of islet cells will ensure at least the presence of glucagon and therefore reducing the potential for life threatening swings in glucose control. And the chance of malignancy is nullified altogether.

While TP-AIT does represent a potentially good treatment option for chronic pancreatitis there has not been a universal uptake of this treatment to consider it the standard of care. In part the procedure is considered to be highly invasive. However this is typically not weighed against the impact of no treatment for chronic pancreatitis. Another reason why the validity of the procedure has been questioned is the concept of insulin free survival or the proportion of people who remain euglycemic without insulin support.

As a major indication of the success of TP-AIT, pain relief rate post TP-AIT ranges from 73% to 90%^{7,15}. The insulin independence rate ranges from 27% to 64% post TP-AIT^{15,25}. The improvement of patient quality of life has been reported in many different studies^{15,26-28}. It is therefore a misconception, as we have shown that patients almost always have a significant islet cell loss even prior to TP-AIT as a result of chronic inflammation and fibrosis²⁹. And it can be argued that if all patients were insulin free after TP-AIT then one could question whether the original diagnosis was indeed chronic pancreatitis.

In view of this we reviewed the literature to evaluate the success of this procedure being addressed considering the "3Ps".

PAIN CONTROL AND QUALITY OF LIFE

Many articles did address this issue. Pain control was documented in the form of reduction in the opiate dosage. Two studies have documented that the morphine requirement after surgery is reduced^{2,30}. Quality of life was addressed using the SF-36 and McGill pain questionnaires, and Visual Analogue Scale. Patients were followed with surveys administered at 1 month, 6 months, and 1 year to evaluate changes in their quality of life and pain experienced. Significant improvement was reported in all components of every questionnaire within a year after surgery. Furthermore, patient reported mean scores on quality of life were found to fall within the range of the general population^{7,15,31-33}.

Many patients with chronic pancreatitis have repeated hospital admission due to pain from acute on chronic pancreatitis. For example, according to the study by Mullady et al³⁴ > 90% of patients had been hospitalized on at least one occasion in their lifetime for pain related to chronic pancreatitis. In addition > 25% of the chronic pancreatitis patients were on disability benefit and patients with constant pain were more likely to miss over 4 days of work or school per month than patients with intermittent pain.

PREVENTION OF BRITTLE DIABETES

There are 21 million of patients suffering from type 1 or 2 DM in the United State (National Diabetes Statistics Report, 2014, www.cdc.gov). All of them are treated with some form of either insulin replacement or agents which would control excess of sugar in blood trying to get them euglycemic. Maintaining normoglycemia prevent or delays their end organ damage i.e. complications like retinopathy, nephropathy, cardiac and vascular complications. Hence if even with low dose of insulin if good euglycemia levels can be maintained than these fearful complications could be delayed. Also, most chronic pancreatitis patients are reported to become diabetic with an onset about five years after the initial diagnosis, as the disease progresses³⁵⁻³⁷, and the only difference between them and pancreatectomised patients would be preservation of glucagon function preventing hypoglycemic deaths, a goal that can be achieved by TP-AIT. Recently described, continuous glucose monitoring analysis as a predictor of islet yield and insulin requirements in autologous islet transplantation can also be used for post-operative monitoring and documenting successful outcome³⁸.

PREVENTION OF PANCREATIC CANCER

There is a 15-fold risk of pancreatic cancer for patients with chronic pancreatitis who are alcoholics and a 40 percent lifetime risk for those with hereditary disease³⁹. Usually cancer develops after prolonged period of suffering from the disease with advanced fibrosis. And data is not clear about how many developed DM during the process. TP-AIT would ameliorate the risk of cancer. There are no reports about the incidental finding of cancer in patients who underwent the procedure. It would be interesting to estimate the change in the risk of cancer and death by implementing this procedure.

FUTURE DEVELOPMENTS

There has been significant progress at all level from the clinical to basic science. Clinically progress has been made in the selection of patients, better predic-

tion of islet yield preoperatively^{29,40}, modifying techniques of surgery to reduce ischemia and surgery induced damage during pancreatectomy to improve islet yield⁴¹, introduction of minimally invasive surgery⁴², availability of standard operating procedures of human islet isolation⁴³⁻⁶⁰, and understanding the host environment which potentially can effect results⁶¹. At the same time progress has been made in islet processing technology that have resulted in the observed improvement of the clinical results and post transplant islet function^{62,63}, use of anticoagulation, and anti-inflammatory strategies to enhance engraftment^{64,65}. In this regard, since Hering et al⁶⁶ applied anti-TNF-alpha blockade in the peritransplant period, many centers have adopted this approach in order to improve early engraftment of human islet graft. Interestingly, Glucagon-like peptide 1 (GLP-1) analogues, especially have been drawing clinician's attention as a means to facilitate islet engraftment⁶⁷⁻⁷⁰. This encouraging achievement in human islet allogeneic graft will bring a bright hope to human islet autotransplant as well. Indications of the procedure are expanding beyond the treatment of chronic pancreatitis to the select cases of neoplasms⁷¹.

CONFLICT OF INTEREST:

The authors have no potential conflict of interest.

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