

REVIEW ARTICLE

Overview of Pancreas Transplantation

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ABSTRACT

According to global report on diabetes by world health organization 1.5 million deaths were directly caused by diabetes in 2012. Pancreas transplantation is the best known treatment for diabetes. Purpose of this review is to give an overview of pancreas transplantation and after a detailed introduction, develop a basic understanding of pancreas transplantation. An overview of the related literature will be assessed and a brief history of pancreas transplantation along with three types of pancreas transplantation (SPKT, PAK, PTA), will be presented. We will elucidate the factors on how surgical procedure for procurement of pancreatic graft is carried out simultaneously with other organs, in three steps. In the recipient part we describe exocrine drainage of pancreatic graft systemic-bladder technique and systemic enteric technique (surgical procedure with different advantages and disadvantages briefly described in the article). While for endocrine drainage there will be presented two widely used techniques and systemic enteric and portal enteric. Immunosuppression for pancreas transplantation induction and maintenance therapy are recently the most used ones. Corticosteroids and steroid free management are under debate in recent years. In 50 years of transplant history there is no gold standard immunosuppression regimen. Although outcomes of pancreas transplantation improved in last decades, there is a decline in number of transplantation. This review is helpful to make a basic understanding of pancreas transplantation for new surgeons.

INTRODUCTION

According to global report on diabetes by world health organization 1.5 million deaths were directly caused by diabetes in 2012 [1]. More than 8% of total health budget is spent on diabetes [2]. Beside this secondary complications from diabetes involve a number of micro and macro vascular complications such are diabetic nephropathy, neuropathy, and retinopathy [3, 4, 5]. End stage renal disease is one of the most significant complication from diabetes [6]. Data received from 54 countries suggested that at least 80% cases of end-stage renal disease (ERSD) are because of diabetes, hypertension or a combination of both hypertension and diabetes [7]. Although after the discovery of insulin in 1922, prognosis of diabetes was shifted from lethal to a chronic disease, still it just delays the progression of secondary complications. Today pancreas transplantation is the most reliable treatment to establish normal glucose levels [8] in patients with type 1 diabetes [9, 10, 11]. Improve quality of life by restoring endogenous insulin secretion and prevention from secondary complications [12, 13, 14]. In the end, it also

minimize the risk of hypoglycemia in patients with type 1 diabetes [15].

History

Pancreas transplantation was for the first time performed in December 1966 by William Kelly and Richard Lillehei at the university of Minnesota, where they transplanted pancreas along with kidney to treat a diabetic uremic female patient and managed to get rid from exogenous insulin for 6 days and later this transplant was rejected [16]. In China pancreas transplantation was performed for the first time on the 22nd of December 1982 [17].

With the improvements in immunosuppressive treatment, surgical technique and preservation of organs, in the successive 1980's period, there was a significant improvement in pancreas transplantation resulting in an increase in the number of transplants [18, 19].

Methods of Pancreas Transplantation

There are 3 methods of solid organ and pancreas transplantation. The first and most performed is where pancreas transplantation is carried out at the same time with kidney, also known as simultaneous pancreas and kidney transplantation (SPK). It is a long surgical procedure. It is treatment of choice for the patients with type 1 diabetes suffering from end stage renal disease [20]. Basic reason for SPKT being common is that the patients are already on immunosuppressive therapy along with the fact that a minor risk of surgical procedure addition benefit can be obtained.

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Pancreas transplantation after kidney (PAK) is another way for pancreas transplantation where a pancreatic allograft is transplanted after kidney transplantation [21]. This method is highly recommended for diabetic patients having successful kidney transplant [22]. With this procedure patient have to go through surgical risk twice.

Pancreas transplantation alone (PTA) is the third recommended procedure for pancreas transplantation, where just pancreas transplantation alone is showing good results [23]. This is the least performed method of pancreatic transplantation but recently coming with good results. Pancreatic islet cell transplantation is another option in practice for the treatment of type one diabetes [24].

Overall percentage of pancreas transplantations performed is 80% SPK, 15% PAK while PTA are 5% [25].

SURGICAL TECHNIQUE

Donor

Procurement of pancreatic graft is done along with other multiple intra-abdominal organs transplantation. This surgery is executed with a unique technique along with liver *en bloc* [26]. Performed in three steps, first of all dissection is done with intact circulation, then organs are cooled in situ with IV transfusion and heparinized (after that liver and pancreata are recovered together while intestines are removed separately) [27, 28]. In the third step organs are prepared for transplantation on back table surgery pancreato-duodenal graft is isolated by removing spleen, (for pancreatic exocrine secretions) and the duodenal segment shortened. What will follow is the suture and invagination of duodenal borders, mobilization of portal vein and vascular Y graft reconstruction. After removal, pancreata and other vascular grafts must be immersed in Belzer-UW solution.

Recipient

Exocrine drainage of pancreatic graft is always a debate between transplant surgeons and this lead to a large number of variations in the expletation of the surgery, all over the years.

Surgical aspect of recipient: There are two techniques for the pancreas exocrine secretions named: systemic-bladder technique and systemic-enteric technique for portal venous delivery of insulin. Enteric drainage of exocrine secretions come up with another technique called portal-enteric technique [29].

Bladder drainage of exocrine secretions systemic bladder technique was very common during 1980s [30]. With this technique donor duodenum is anastomosed to viseral dome by using a 2 layered hand sew dn technique or a circular stapled [31]. This technique is safe, sterile and easy to perform. There are two major advantages of this technique. First one is that, bladder-duodenal anastomosis leakage can be managed by urinary catheter [32] and urinary amylase. Second one, that Insulin can

be measured as an important indication for early graft rejection [33, 34]. On the other hand there are also a number of complications like reflux pancreatitis, urinary tract infection and haematuria, all associated with bladder drainage due to bicarbonates lose [35].

Enteric Drainage of Exocrine Secretions

With this technique duodenum of donor is anastomosed with bowel of recipient (proximal jejunum or distal ileum). Gastric and duodenal drainage are also used [36, 37, 38]. Anastomosis is stapled in a linear fashion [39], with a circular device [40] or hand sewn. A number of urinary tract complications were reported with bladder drainage caused by non-physiological drainage of pancreatic enzymes into the urinary tract [41]. Surgeons report enteric drainage much safer as compared to bladder drainage [42, 43].

To manage the endocrine drainage there are two widely used techniques: systemic enteric and portal enteric drainage. Portal drainage is mostly used with enteric exocrine drainage. Donor portal vein and recipient splenic vein are end to side anastomosed [44]; distal splenic vein of donor and portal vein of recipient with bladder drainage [45], or draining transplanted pancreas converge directly in mesenteric vein [46]. Portal venous drainage is said to be more physiological whereas enteric drainage is associated with hyperinsulinemia [47]. Different studies showed same long term and short term outcomes of pancreatic transplantation with portal venous drainage and enteric venous drainage [48, 49]. Systemic venous drainage is the most commonly used technique in America [50].

Immunosuppression

Regarding immunosuppression for pancreatic transplantation, induction [51] and maintenance therapy [52] are most commonly used recently. Anti lymphocyte serum such as daclizumab (anti CD25 (interleukin-2 receptor) monoclonal antibody) and basiliximab are used for induction therapy. While prednisone (corticosteroid), mycophenolate mofetil (anti metabolite), and tacrolimus (calcineurin inhibitor) are used for maintenance therapy.

SRTR data show that trend for induction therapy has shifted towards T-cell depleting induction agents, such as alemtuzumab and thymoglobulin instead of interleukin-2 receptor antagonist like basiliximab [53]. Corticosteroids management and steroid free immunosuppression has been at the center of the debate, in recent years. As corticosteroids are major cause for post-transplant, hyperglycemia, hyperlipidemia and hypertension increase cardiovascular risk in recipient [54]. UNSO database showed that there is an higher evolving risk of infectious complications with steroid maintenance therapy as compared to steroid free therapy [55]. In 2000 mTOR inhibitors were introduced for immunosuppression of pancreatic transplantation [56], such as Everolimus and sirolimus, both found to be effective and SPKT particularly to avoid renal complications and an alternative for MMF to reduce complications caused by MMF such as leucopenia

and GI toxicity. Costimulatory blockade agents like Belatacept are least for immunosuppression of pancreatic graft recipient. In the 50-year-history of pancreas transplantation, researchers were unable establish a gold immunosuppressive regimen standard.

Complications

Technical failure is the primary complication for a graft failure within the first three months after transplantation, vascular thrombosis account for half of the pancreatic graft lose [57] that is: 50%, pancreatitis 20%, infections 18%, fistula 6.5% Bleeding accounts for 2.4% for total pancreatic graft failure [58]. The risk factors associated with surgical complications are: age factor(aging more than 45 for donor or recipient) and cold ischemia lasting more than 24 hours [59]. Medical history of recipient also play an important role in survival of pancreatic graft. About 10-25% pancreatic transplant with bladder drainage of exocrine secretions need to be converted to enteric drainage [60]. Enteric drainage(intestinal leakage) is one of the significant postoperative complication observed in 5-8% of graft, treated by removal of pancreatic graft [61]. Even though there are advancements in immunosuppression and antibiotic therapy, infections still are the major cause for mortality and morbidity in pancreas transplantation. An early detection of infectious agent and etiology of infection can be helpful to improve graft survival.

Scope

Outcomes of pancreas transplantation improved in last five decades but there was a slight decline in number of transplants after 2004 [62, 63]. Five year patient survival rates for all three groups are approximately 90% and for ten years 70%. Insulin independence for 5 years is 73% in SPK, 64% in PAK and 53% in PAT. Half life of pancreatic graft is 10-15 years. Therefore a lot of work is needed to be done on pancreas transplantation. Increase the number of transplantation centers should be the urge of the authorities, as until now pancreas transplantation is limited to a few centers and only upcoming surgeons are trained to perform the surgery. Especially in Asia and developing countries all over the world. As diabetes data suggest, there is a huge gap to be filled between large number of patients and lack of surgical skills as well as scarcity of transplantation centers. Although liver and kidney transplantation are very common but pancreas transplantation is limited to some countries and a few centers.

CONCLUSION

Pancreas transplantation is the most effective treatment for diabetes. Better surgical method can be chosen to minimize the surgical complications with enteric or bladder drainage. Advancement in immunosuppression improved life after transplantation. There is an improved quality of life in uremic diabetic patient.

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Conflict of interest

Authors report no conflicts of interest.

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