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ORIGINAL ARTICLE

Current practices of donor pancreas allocation in the UK: future implications for pancreas and islet transplantation*

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Summary

Recent refinements in technique mean islet cell transplantation offers the chance of a cure to an increasing patient cohort with diabetes. Such developments put pressure upon the scarce resource of donor organs, with potential competition between the modalities of cellular and solid organ transplantation. This questionnaire based study examines current patterns of donor pancreas procurement and use. Reasons for non procurement are studied together with the attitudes of transplant professionals to pancreas allocation. The minority of potentially useful pancreata are currently made available to either whole pancreas or islet transplant programs. Whilst professionals appreciate the role of each modality, there is a need to define criteria for pancreas allocation to avoid under use of donor organs.

Introduction

Historically the only treatment for patients with type 1 diabetes has been subcutaneous insulin injections. It is now well established that the use of daily insulin injections cannot exert the same degree of control on blood glucose as functioning islets *in vivo*. Even strict exogenous insulin use does not completely alleviate the long-term vascular and neurological complications associated with diabetes mellitus [1].

For selected patients transplantation can restore insulin independence but at the expense of immunosuppression. For diabetic patients with end-stage renal failure who can withstand the complications of surgery, whole vascularized pancreas transplantation (VPT) has become the gold standard treatment to achieve insulin independence [2]. The recurrence of diabetic nephropathy in a simultaneously transplanted kidney can be delayed by simultaneous pancreas and kidney transplantation (SPK) [3] in addition to amelioration of neuropathy [4]. More importantly, mortality can be significantly reduced when compared with kidney transplantation alone [5].

In comparison recent advances in islet cell transplantation now make it a realistic treatment modality in a highly selected groups of type 1 diabetic patients [6].

A recent Immune Tolerance Network multi-centre trial of islet transplantation alone (ITA) in type 1 diabetic patients has demonstrated the efficacy and reproducibility of this technique with 56% remaining insulin independent at 1 year [7]. Nevertheless one of the drawbacks of this technique is the need for sequential transplants, requiring islet preparations from at least two organ

donors, to achieve an adequate transplanted islet mass for insulin independence [6].

Whilst some centres are able to obtain adequate numbers of islets from single donors [8], the majority of patients still require two or more donor pancreata. With the current well recognized lack of organ donors for transplantation it is likely that, until the efficiency of islet isolation is improved, the procedure will not be made available to all those who need it. A recent report from Madison has highlighted some of these issues by identifying an under utilization of the human donor pancreas in the United States [9]. Moreover, as the newly emerging modality of ITA is demonstrating comparable results to VPT the transplant community faces a potential conflict over donor organ allocation between islet and whole pancreas programmes. The aim of this study was firstly, to investigate the patterns of donor pancreas allocation and secondly, to evaluate the opinions of transplant healthcare professionals with respect to either VPT or ITA in the United Kingdom.

Methods

A retrospective analysis of UK Transplant data for the year 2000–2001 was undertaken to examine current rates of donor pancreas procurement, allocation and utilization. Such data was gathered contemporaneously at organ retrieval from donor transplant coordinators and that held on the UK Transplant database. The number of non-procured donor pancreata were obtained together with reasons for nonprocurement.

A questionnaire was designed to examine pancreas transplantation activity amongst UK transplant centres, current donor pancreas consent issues and opinions regarding ITA, VPT and donor pancreas allocation. Questionnaires were distributed to all registered UK transplant consultants and transplant coordinators in 35 centres. After the initial distribution, the questionnaire was resent to nonresponders to try to increase the response rate.

Briefly, donor human pancreata considered suitable for whole VPT range between 10 and 49 years although this is considered restrictive by others [10] and in the authors centre between 10 and 70 years for islet transplantation. All donors must be nondiabetic with a blood glucose <11 mmol/l.

Results

During the 12 month study period 704 multi-organ procurements took place in the United Kingdom. In total 181 donor human pancreata were procured (25.7%). Between the age ranges 0 and 10 years or >70 years 34 procurements were performed and were therefore not suitable for either VPT or ITA (Table 1). Therefore 178 pancreas were potentially suitable for clinical use from a donor pool of 670 (26.6%). Of the 523 where pancreas donation was not performed; 442 (84.5%) were never offered for retrieval by the donor centre, in addition 81 (15%) were offered for retrieval but were not procured. The reasons for failure to offer and retrieve the donor pancreas are summarized in Tables 2 and 3, respectively.

From the 178 successfully procured pancreata; 47 (26.4%) were used as whole pancreas grafts – 40 (85%) were used for SPK procedures, six (13%) PTA and one (2%) for PAK a further five were allocated and accepted for whole pancreas transplantation but were not transplanted. Reasons for the failure to transplant were not documented.

In terms of allocation for research 48 (27%) were predominantly for experimental islet isolation. Fifty (28%) successfully procured pancreata were declined for both clinical transplantation and research on the basis of donor age. Forty-six (92%) of these declined organs were in the

Table 1. Distribution of multi-organ procurements between age cohorts.

Age stratum (years)	Number of multi-organ donors	Number of donated pancreata (%)
0–9	21	3 (14)
10–19	74	18 (24)
20–29	90	27 (30)
30–39	117	51 (44)
40–49	146	34 (23)
50–59	172	37 (22)
60–69	71	11 (15)
70+	13	0 (0)
Total	704	181 (26)

Table 2. Reasons stated why the pancreas was not offered.

Reason cited for not offering	Number of donor pancreata (%)
Consent factors	
No consent sought	2 (0.5)
Consent refused by donor family	169 (38)
Consent refused by 3rd party	5 (1)
Donor factors	
Donor age	189 (43)
Donor medical history/virology/cause of death	27 (6)
Donor medication	7 (4)
Unstable donor/non-heart beating donor (NHBD)	9 (2)
Damaged organ	3 (0.6)
Retrieval factors	
Lack of time	3 (0.6)
Unknown	28 (6.3)
Total	442

Table 3. Reasons stated for nonprocurement.

Reason cited for nonprocurement	Number of donor pancreata (%)
Donor factors	
Donor age	5 (6)
Donor medical history/virology/cause of death	3 (4)
Donor BMI	3 (4)
Poor organ function/damage	5 (6)
Donor medication	2 (2)
Recipient factors	
No suitable recipient	31 (38)
Retrieval factors	
Staffing/beds/lack of time	22 (27)
Unknown	10 (12)
Total	81

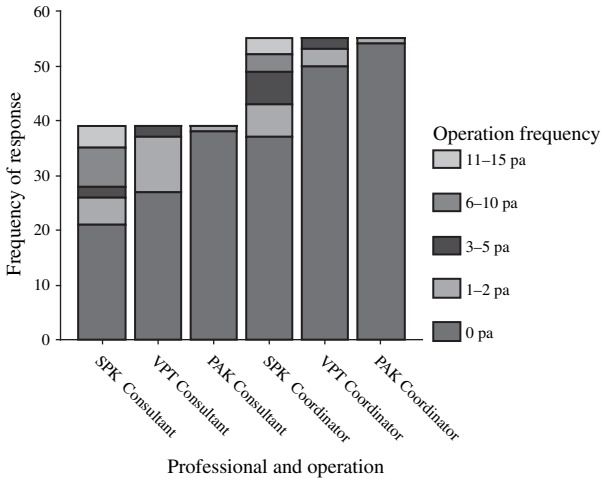

Figure 1 Professionals perception of whole pancreas transplant activity.

10–49 years age range suitable for either islet or whole pancreas transplantation, and all were in the extended 10–69 years age range suitable for islet isolation by itself. Twenty (11%) successfully procured pancreata were not allocated to clinical transplantation or research because of staffing or logistical factors at the receiving centres. The reasons for declining the offer of a procured organ were unknown in 13 (7%) cases.

Questionnaires were distributed amongst consultant transplant surgeons ($n = 75$) and transplant coordinators ($n = 103$) in 35 UK transplant centres. Responses were obtained from 33 centres (94%) and response rates from consultants and coordinators after two mail shots were 96% ($n = 72$) and 93% ($n = 96$), respectively. Ten responders returned blank questionnaires (three consultants and seven coordinators), hence a valid response was given by 92% ($n = 69$) of consultants and 86% ($n = 89$) of coordinators.

Pancreas transplant activity

Thirteen centres (39%) stated they had an active whole pancreas transplant programme. Thirty-nine (57%) consultants and 55 (62%) coordinators were involved in whole pancreas programmes. Yet during the study period only four centres performed more than four whole pancreas transplants. In comparison 21 (54%) consultants and 37 (67%) coordinators involved in such programmes answered that no SPK procedures were being performed in their centre and higher levels of inactivity were cited for VPT alone and PAK (Fig. 1).

Consent, pancreas procurement and allocation practices

Forty-six (67%) consultants and 65 (73%) of coordinators stated that consent for pancreas retrieval should be a routine part of a multi-organ donation. Thirty-seven (56%) consultants and 65 (73%) coordinators stated that seeking consent for both clinical transplantation and research should form part of the standard approach to a donor family.

Opinions were split amongst the surgeons regarding the optimal timing and method of pancreas removal. Thirty-five (51%) consultants felt that the pancreas should be retrieved after the liver but prior to kidney retrieval; 16 (23%) after the liver and kidneys; seven (10%) using an *en bloc* technique to remove both liver and pancreas and two (3%) before both liver and kidneys. Eleven (15%) stated that they had no knowledge of the optimal time or technique of pancreas procurement.

Thirty-eight consultants (55%) and 40 coordinators (45%) felt that all potential donor pancreata should be allocated for a whole pancreas transplant because it is an established clinical procedure. Also 46 (67%) consultants and 47 (53%) coordinators stated that SPK remains the optimal treatment for a young type 1 diabetic patient with end-stage diabetic nephropathy, 20 (22%) coordinators were unsure of the role of this treatment in such patients.

Conflicting opinions were apparent regarding allocation of pancreata based on donor criteria. Fifty-six (81%) consultants stated pancreata from older organ donors (>50 years) should be used for islet transplantation, eight (11%) disagreed and six (8%) were unsure. Thirty-eight (55%) of all consultants stated that pancreata from organ donors with a high body mass index (BMI; >30 kg/m^2) should be preferentially allocated to islet transplantation whereas 21 (28%) disagreed and 13 (17%) were unsure. In comparison only 18 (25%) stated that a pancreas retrieved from a young lean organ donor would not be suitable for a whole pancreas transplant and six (9%)

were unsure. Finally, 18 (25%) consultants felt that a previously nondiabetic donor with hyperglycaemia would not be a suitable pancreas donor. Fifty (66%) responding consultants thought such organs should still be procured for clinical use, six (9%) were unsure of the appropriate allocation of such donors.

Opinions regarding islet transplantation

Thirty-two (47%) consultants and 32 (35%) coordinators stated that their centre was likely to start an islet transplant programme. This represented a positive response from at least one consultant and coordinator from 16 (45%) centres. The majority of both consultants and coordinators agree that islet transplantation has a future in the treatment of diabetes. Sixty-six (95%) consultants and 70 (78%) coordinators thought that islet transplantation could offer a potential cure for diabetes. Forty-six (67%) consultants would recommend an islet and kidney transplant to diabetic patients with end-stage diabetic nephropathy, and 55 (80%) would recommend an ITA for diabetic patients with severe hypoglycaemic unawareness using the Edmonton protocol.

Discussion

This study used a retrospective analysis of UK Transplant data to examine current practices of human pancreas procurement and allocation for transplantation. A postal questionnaire was also used to evaluate current practice and opinions of those involved in human pancreas procurement, allocation and transplantation. During the period 2000–2001 an unacceptably low rate (26.6%) of pancreas procurement from suitably aged donors was observed. During the same period rates of procurement for either heart (58%), lung (41%), liver (71%) or kidney transplantation (82%) were significantly higher [11]. This compares to a recent European study from the Geneva group suggesting that only 10% of all donors are suitable for pancreas transplantation whereas 38% for potential islet transplantation [12]. Failure to obtain the donor pancreas was overwhelmingly because of donor factors thought to be detrimental to pancreatic function.

Donor age was cited as the main reason for not offering or procuring the pancreas in 37% of cases, despite 60% of donors lying in the 10–49 years age range where the majority are suitable for whole pancreas transplants [2,10] and all worth a trial of digestion for clinical islet isolation [13,14]. If the age criteria were extended to 70 years to include organs suitable for clinical islet isolation 95% of the multi-organ procurements could have been potentially used. Of those pancreata successfully procured a high proportion (28%) were declined for both clinical transplantation and research programmes on the grounds of unsuitable donor age. Although the majority of those responding to the questionnaire agreed with the allocation of the older donor pancreas (>50 years) to islet programmes, a significant proportion of responding consultants disagreed (11%) or were unsure (8%). It would appear that donor age is a frequently cited reason for nonprocurement despite the majority of donors being of an appropriate age.

Donor age correlates with both islet yield and function (P.Y. Benhamou, 1994, unpublished data, Department of Surgery UCLA School of Medicine 90024–7036.]. Similarly, donor age also correlates with function after VPT [15]. For example, when the human pancreas is procured from donors aged 55 and over islet yields are high and their stimulated function is comparable with those isolated from younger organ donors [13]. In contrast once donor age exceeds 45 years or more there is an increased risk of poor glycaemic control and premature loss of graft function in whole pancreas transplants [15,16]. It seems logical therefore, that procured pancreata from normoglycaemic donors can be allocated based primarily upon donor age. Where the donor is over 45 years and the pancreas is turned down for whole organ transplantation it should be offered for islet isolation unless contra-indicated by other co-morbidity such as diabetes, haemodynamic instability or prolonged ITU stay, adverse donor medical history or contra-indicated medications [14]. These factors were cited in 9% as cause for nonprocurement.

In a small number of donors hyperglycaemia (1.7%) and obesity (0.5%) were given as reasons for failure to retrieve. Questionnaire responses showed inconsistencies amongst transplant professionals regarding the allocation of such donor organs. Several studies have examined the potential of the human pancreas from marginal donors. After pancreas transplantation, the use of a pancreas from a donor with serum hyperglycaemia is associated with a poor functional outcome [17]. Similarly the yield of islets from such donor pancreata is also poor [13,14].

Although 55% of consultants agreed with the allocation of the human pancreas from obese (BMI >30) donors for islet isolation, a large proportion (28%) disagreed or were unsure (17%). Donor obesity has shown no detrimental effect upon islet yield, viability or function [13,14]. Whereas donor obesity has been associated with increased risk of recipient abdominal infection following whole pancreas transplantation [18].

Optimal pancreas retrieval, timing and technique is known to be critical to the function of pancreas allografts and the attainment of good islet yield, function and viability [19]. The Edmonton group advocate local retrieval teams, packing of the lesser sac with ice immediately after

aortic cross clamping and removal of the pancreas *en bloc* or even before the liver [6]. Without packing core temperature *in situ* can rise to 18 °C. Such practices have not been widely adopted in the UK. It would appear there is no agreement as to what is the best method for pancreas retrieval. It is likely that even when the pancreas is procured successfully the surgical techniques used may not be of optimal quality for either whole pancreas transplantation or islet isolation. Although the precise number is speculative, from the authors survey 11% were procured and not used but the reasons cited were not specifically relating to a suboptimal organ. Comparisons can be made with renal transplantation where 19% of all kidneys retrieved are damaged but only 1% overall are not suitable for transplantation [20]. Clearly the retrieval process is critical to maximizing organ usage after donation. This issue has been addressed by the British Transplantation Society. Organ retrieval workshops and courses are now available for transplant trainees in the UK but are not compulsory.

The duration of pancreatic cold ischaemia is a further factor limiting post-transplant function after VPT [2,15] in addition to islet yield and viability after islet isolation. When cold ischaemic time is greater than 16 h extremely poor islet yields are isolated [21]. Islet yields can be optimized by limiting cold ischaemic times to an 8 h maximum [22]. There is limited evidence that a short period of cold ischaemic storage is beneficial for subsequent islet isolation by permitting endogenous pancreatic enzyme activation. Clearly to optimize cold ischaemia there has to be effective communication between the retrieving and isolating centres to facilitate rapid transportation of the organ to the transplant centre.

In recent years there have been a number of improvements in pancreas preservation techniques. The two-layer method of pancreas preservation [23], combining cold storage and the high oxygen carriage capacity of perfluorochemical, is thought to result in a degree of pancreatic resuscitation after prolonged cold ischaemia. Recent studies have also shown the ability of this technique to allow isolation of a high number of viable islets from organs with a short period of warm ischaemia [24]. Furthermore higher islet yields can be obtained for marginal human pancreata [25] and those with cold ischaemic times up to 16 h [26]. This clearly has implications for future islet transplantation in further expanding the pool of potentially useful donor pancreata.

Consenting donor families for use of organs for either organ research or clinical practice is a difficult issue. The majority of consultants and coordinators stated that consent for pancreas retrieval for both clinical transplantation and research forms a routine part of their practice. Yet it is clear from this study that consent is frequently declined by donor families or not offered at all. Whilst respecting the wishes of the bereaved families should always remain the highest priority at multi-organ donation, the high rate of refusal may arise from the need for research consent prior to islet isolation. There is frequently, a reluctance to consent for research, and many donor families are perhaps understandably keen only for organs to be procured for clinical use [27,28]. The recent improvements of islet transplantation should justify the technique as current clinical practice in designated clinical islet transplant centres, and once it has shown to be reproducible and efficacious in such centres the stigma of a research technique should be removed. The Eurotransplant [29,30] and GRAGIL [31] collaborations have already demonstrated that, within the bounds of European legislation [32], high numbers of donor organs may be procured and successfully used for islet isolation. Indeed in Edmonton, Canada islet transplantation is now regarded a recognized clinical procedure reimbursed by insurance companies and health authorities. It is therefore hoped that this success will lead to an expansion of donor referrals.

Currently donor pancreata are being under utilized by both whole pancreas and islet transplantation programmes. Despite 13 centres claiming involvement in whole pancreas transplant programmes, the current levels of whole pancreas transplant activity are low (*vide supra*). Interest and enthusiasm for islet transplantation remains high with a large proportion of consultants and coordinators advocating islet transplantation as a treatment in appropriately selected type 1 diabetic recipients. Nevertheless this may have a potentially detrimental effect on islet transplantation. It was stated that at least 16 centres were likely to start a clinical islet transplant programme. Based on current rates of donation (131 per annum), and the belief that only one-third to 50% of all islet isolation yield a suitable islet yield for clinical transplantation, and that sequential transplants are required, each centre would perform a maximum of two transplants per annum. Clearly in an era of strict clinical governance this is not acceptable given the potential risks involved.

Despite the restricted application of islet cell transplantation in the UK, the technique has the potential to compete with whole pancreas transplantation. At present all suitable human donor pancreata should be offered for whole organ programmes unless a suitable recipient cannot be identified. There is an urgent need to prevent such conflict by establishing protocols and guidelines for the appropriate allocation of the human pancreas to each modality. This will avoid inappropriate organ placement, the use of suboptimal or marginal organs tissue and the under-utilization of precious human donor pancreas for diabetic patients in need.

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