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Impact of adverse pancreatic injury at surgical procurement upon islet isolation outcome

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Summary

The consequence of a pancreas injury during the procurement for islet isolation purpose is unknown. The goal of this work was to assess the injuries of the pancreata procured for islet isolation, and to determine their effect on the islet yield. Between January 2007 and October 2013, we prospectively documented every injury of the pancreata processed in our centre for islet isolation. Injuries involving the main duct were classified as major, the others as minor. Donors' characteristics and islet yields were compared between the groups of injuries. A pancreas injury was identified in 42 of 452 pancreata received for islet isolation (9.3%). In 15 cases, the injury was major (3.3% of all pancreata). Although a minor injury did not affect the islet yield, a major injury was significantly associated with unfavourable outcomes (postpurification mean islet equivalent of 364 $\pm$ 181, 405 $\pm$ 190 and 230 $\pm$ 115 $\times$ 10^3 for absence of injury, minor injury and major injury, respectively). A major injury was significantly more prevalent in lean and short donors. We recommend assessing the quality of the pancreas in the islet isolation centre before starting the isolation procedure. Each centre should determine its own policy based on its financial resources and on the wait list.

Introduction

Organ or tissue procurement is the first step of any allotransplantation. In the case of intra-abdominal organs, the surgical technique to prepare and recover each organ follows main principles that have been already described in the early 80s [1,2]. Although its concept is simple – to remove undamaged organs with their tributary vessels and ducts as long as possible – its realization can be challenging. The surgeon has potentially to deal with a complex anatomy in unfriendly conditions: unstable patient, remote or foreign hospitals, several procurement teams working at the same time.

A major injury to the procured organ can compromise the further transplant, in particular injuries to the main vessels. The rate and type of injuries related to intra-abdominal organs have already been described, as well as the consequence of the transplant suitability of the injured organ [3–6].

The pancreas procurement for whole organ transplant is particularly challenging, and its discard rate is high [7]. In the case of the pancreas procurement for islet isolation and subsequent transplant, the preservation of the vasculature is not necessary, the collagenase enzyme aiming to digest the pancreas being infused through the main pancreatic duct [8]. Although existing guidelines describe the critical steps for successful whole organ pancreas procurement [9], few data or recommendations exist for the pancreata procured for islet [10]. Dissecting and preparing a pancreas for whole organ transplantation is time–consuming, and such a surgery cannot be proposed as a standard for islet transplantation purpose. On the other hand, an insufficient exposure of the pancreas in the warm phase can induce misrecognitions of the limits of the organ leading to parenchymal tears or a poor cooling of the organ.

To date, no studies exist indicating the frequency, the type and the consequences of injuries affecting the pancreas procured for islets isolation purpose, and the goal of this work was to present these information based on the data collected in the islet isolation facility of our institution.

Patients and methods

Between January 2007 and October 2013, 552 pancreata procured from deceased donors at retrieval hospitals throughout Canada were processed for islet isolation at our clean room facility. Among 552 islet isolation procedures, 100 were performed in the context of experimental clinical trials using isolation methods different from our standard procedure and were excluded from the evaluation. Thus, the remaining 452 pancreata formed the basis of the study.

Upon arrival of the pancreas at our facility, quality of the gland was evaluated in terms of the presence of parenchymal injuries. The parenchymal injuries were classified as major when they did involve the main pancreatic duct and as minor when they did not. All issues related to pancreas recovery reported in the standard procurement forms, if present, were also reviewed. Injuries not related to pancreas parenchyma (i.e. spleen, duodenum and vessels) were not considered in this study. Donor information and islet isolation outcomes were reviewed from all 452 islet isolation batch files. The methods for islet isolation have been described previously [8], but briefly, the weight of the pancreas was recorded before the digestion process, two canulas were inserted in the main duct at the level of the pancreas neck and a cold collagenase solution was perfused. We estimated the distension quality by the collagenase solution by dividing the volume of the collagenase remained in the pancreas at the end of perfusion by the pancreas weight prior to the perfusion. This ratio is represented as the 'pancreas distension index'. The pancreas was cut into small pieces that were introduced in a Ricordi chamber whose content was heated at 37 °C. After the digestion, the pancreas remnant was weighted, and the digested islets were counted before the purification. Islets were isolated from the exocrine tissue using a Ficoll gradient centrifugation. Islets were again counted after this purification and represented the final islet yield.

Continuous variables were expressed as means and standard deviations; dichotomous variables were expressed as natural numbers. When analysed between dichotomous groups, continuous variables were analysed using bilateral *T*-test and dichotomous variables were analysed using chi-square test. Comparisons of continuous variables in more than two groups were made using ANOVA. We performed a linear regression to assess the correlation of the different continuous variables with the postpurification islet yield. A P value <0.05 was considered significant. The statistical analysis was performed using SPSS 17.0 (IBM Corporation, New York, NY, USA).

Results

A pancreas injury was identified in 42 of 452 pancreata received for islet isolation (9.3%). In 15 cases, the injury was major (3.3% of all pancreata).

A minor injury did not affect the islet yields, but a major injury was associated with unfavourable outcome [postpurification islet yields were 364 ± 181, 405 ± 190 and 230 ± 115 × 10^3 islet equivalent (IE) for absence of injury and minor and major injuries, respectively] Fig. 1.

Examples of major tears are shown in Fig. 2 and included complete transection of the body or the tail, partial transection of any segment of the pancreas, and longitudinal injuries involving the Wirsung duct. It was impossible to assess retrospectively at exactly what moment during the procurement the injury had taken place. In none of the cases was a tear of the pancreas mentioned in the procurement report and all injuries were discovered in our islet isolation facility.

The majority of the minor injuries involved the head (n = 9) and the neck (n = 9) followed by the tail (n = 6) and the body (n = 3). The majority of the major injuries involved the head (n = 8) followed by the neck (n = 4) and the body (n = 3). No major injury involved the tail of the pancreas.

Because a major injury was associated with significantly lower yields of islet, while no adverse effect on islet isolation outcome was observed with minor injury, we

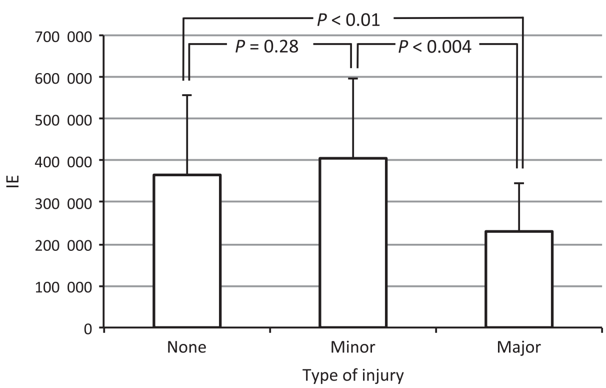

Figure 1 Postpurification islet equivalent (IE) mean yield according to the pancreas injuries during the recovery. The mean IE yield is similar between pancreata procured without injuries and pancreata presenting a minor injury. The IE yield dropped significantly in the major injury group.

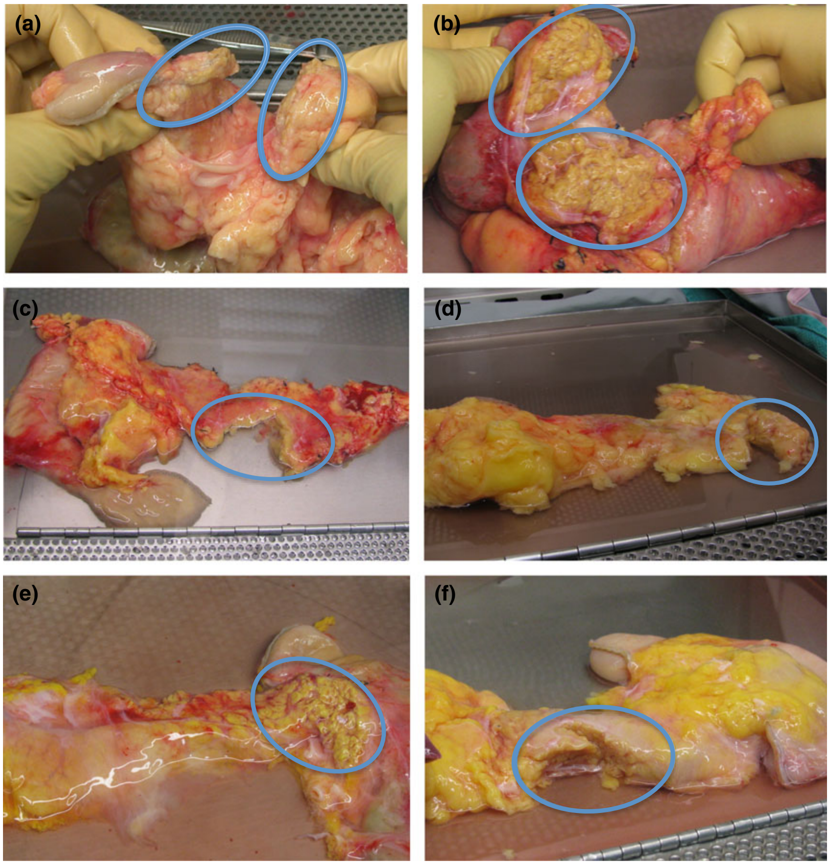

Figure 2 Example of major pancreas tears: (a) Transection of the body (in this particular case, half of the body was accidentally resected using a stapler), (b) Transection of the head, (c) Incomplete transection of the body, (d) Incomplete transection of the tail, (e) Longitudinal tear of the head with substance loss, (f) Complex tear of the body with substance loss. Blue circles highlight the damaged zones.

compared the donor variables in the major injury group versus those in the nonmajor injury group (minor injury or intact pancreas) to identify risk factors for a major injury. The donor variables associated with the presence of a major injury are presented in Table 1. The presence of a major injury was more prevalent in female donors, lighter and shorter donors. The body mass index (BMI) was not associated with a major injury. We assessed if the pancreatic lesion was concordant with the trauma related to death. None of the lesions of the pancreas presented in this work were compatible with a nonsurgical event.

The digestion efficacy [(pancreas weight−undigested pancreas weight)/pancreas weight × 100] was inferior for pancreata with major injury. Interestingly, the pancreas distension index was lower in the pancreata with major injuries compared to the pancreata with minor or no injuries, although the difference was not significant. Given the nature of the injuries, we presumed that a poor distension of the pancreas was associated with enzyme solution leakage through the injured site leading to a worse results in terms of islet yield at prepurification as well as at postpurification. The characteristics of each of the 15 cases of major injury are shown in Table 2.

We assessed in a univariate analysis the factors affecting the islets yield, including the presence of a major injury (Table 3). We performed a linear regression using the postpurification islet yield scale as the dependent variable. We did not introduce the pancreas distension index in the univariate model, as the index is composed of two variables that would introduce bias (the index is inversely influenced by the pancreas weight that has been shown to affect positively the islet yield).

Nine of eleven variables analysed in the univariate regression model were significantly associated with the postpurification islet yield. Two variables were significantly associated with a worse outcome, reflected by negative beta values: the digestion time and a major injury. A long digestion time reflects difficulty in obtaining islets freed from the exocrine tissue during the digestion process.

Donor age, male gender, weight, height, BMI, pancreata weight and percentage of digested pancreata were the seven variables associated with an increased islet yield. The

Table 1. Comparison of characteristics of the donor, procured pancreas and obtained islets between the groups of nondamaged or minor injured pancreata and major damaged pancreata.

		No or minor injury			Major injury			
	Type	*N*	Mean	SD	*N*	Mean	SD	*P*
Donor age			48.3	13.6		51.0	12.9	0.455
Donor gender	Male	236			4			0.037
	Female	201			11			
Donor weight (kg)			80.6	18.7		67.8	8.1	0.009
Donor height (m)			1.72	0.1		1.64	0.1	0.012
Donor BMI			27.4	5.8		25.2	2.9	0.152
Cause of death	Trauma	99			3			0.809
	Nontrauma	338			12			
Cold ischaemia time (h)			9.3	3.8		10.6	3.6	0.214
Pancreas weight (g)			94.5	27.8		83.6	20.2	0.13
Pancreas distension index			1.22	0.48		1.03	0.43	0.128
Pancreas digested* (%)			80.5	12.5		71.5	19.9	0.007
Pancreas digestion time (min)			17.4	5.3		17.5	4.8	0.950
Prepurification islet yield ($\times 10^3$ IE)			544	245		333	154	0.001
Postpurification islet yield ($\times 10^3$ IE)			367	191		230	115	0.008
Islets purity (%)			53.8	16.2		47.8	18.2	0.17
Islets viability (%)			82.6	8.1		81.2	10.3	0.535
Islets pellet volume (ml)			3.95	1.5		3.25	1.1	0.092

*Pancreas digested (%) = (pancreas weight−undigested pancreas weight)/pancreas weight × 100.

donor's weight was the variables with the strongest association with the postpurification islet yield (beta value 0.488).

Although the presence of a major injury was significantly associated with unfavourable outcome, we renounced to perform a multivariate analysis due to the low number a major injuries, insufficient for the purpose of a multivariate analysis.

During the study period, there were no cases where injuries identified on visual inspection led to a decision not proceed with isolation procedure, even in cases of major injury. Indeed, three islet preparations from pancreata with a major injury were successfully transplanted into patients with type 1 diabetes. Whenever possible, we performed a salvage procedure using additional catheters to perfuse the damaged pancreas as shown in Fig. 3.

Discussion

The present work is the first report of the rate of surgical injuries to the pancreata procured for islet isolation purposes. Although the injuries of the main vessels are a frequent reason to decline the organ in the case of whole pancreas transplantation [7], injuries of the parenchyma may negatively affect the outcome of islet transplantation by reducing the yield of islet isolation procedures. The cause of decreased islet yield related to a major injury was not directly assessed in this study. We speculate that a major injury would affect the islet isolation in part by amputating the gland and by preventing adequate perfusion with collagenase. We made an estimate of pancreas perfusion efficiency by generating a pancreas distension index, reflecting the amount of collagenase remaining in the pancreas after perfusion. This index is indicative as well as the other ways to assess perfusion (visual semi-quantitative scale, pressure and flow), but has never been validated in a model. We would therefore remain cautious in the interpretation of its values.

In the present series, only a major injury, involving the main pancreatic duct, was associated with a poor islet yield. However, any tear reflects an unsafe dissection of the pancreas, except in the case where preservation of a right replaced hepatic artery crossing through the pancreas, during liver procurement, requires sacrifice of the pancreas. In none of the cases was such a scenario reported by the procuring surgeon. Thus, based on the procurement reports, we would assume that most of the tears were unrecognized at the time of the surgery. Because injuries were not intentional, we can also assume that many minor injuries did not involve the main duct only by chance. We therefore recommend the highest level of caution when dissecting the pancreas, using the same technique as for whole organ transplantation procurement during the cold phase.

Interestingly, major injuries occurred more frequently in lean and female donors. This is in contrast to the technical challenge represented by the obesity which might have been expected to explain some of the surgical injuries. Intra-abdominal obesity is more commonly present in male patients and is reported by most of the surgeons as an

Table 2. Characteristics of the 15 pancreases with major injuries and of their islet isolation. The prepurification islet yield for the pancreas number 15 was too low to proceed to purification.

Pancreas Nb	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Donor age (years)	56	20	67	51	57	49	53	28	55	49	67	54	62	42	55
Donor gender	F	M	F	F	M	F	F	M	F	F	F	F	F	M	F
Donor weight (kg)	57	68	62	60	80	68	67	74	57	82	60	68	80	67	68
Donor height (m)	1.67	1.57	1.6	1.73	1.7	1.65	1.55	1.74	1.62	1.67	1.52	1.64	1.75	1.7	1.53
Donor BMI	20.4	27.6	24.2	20	27.7	25	27.8	24.4	21.7	29.4	26	25.3	26.1	23	29
Cold ischaemia time (h)	5	12	10	5	9	13	12	12	16	5	11	14	13	14	9
Pancreas weight (gr)	103	63	65	92	86	106	64	53	69	102	86	95	125	80	67
Pancreas distension index	0.49	0.95	0.77	0.54	1.28	0.66	1.57	1.69	1.45	0.99	1.74	0.53	0.80	1.25	0.75
Pancreas digested* (%)	65	97	32	94	34	79	83	87	86	87	75	60	66	73	56
Pancreas digestion time (min)	25	25	15	14	13	10	23	13	24	17	17	16	19	17	15
Undigested pancreatic mass (gr)	36	2	45	5	57	22	11	7	10	13	22	38	43	21	30
Prepurification islet yield ($\times 10^3$ IE)	126 753	168 012	111 457	483 579	212 823	317 478	403 211	376 338	504 177	423 783	456 161	530 336	414 329	396 007	74 057
Postpurification islet yield ($\times 10^3$ IE)	39 078	79 363	94 323	143 678	179 510	187 460	234 307	240 470	256 257	327 818	335 338	342 280	371 671	394 712	–
Islets viability (%)	71	82	63	71	96	81	73	71	85	90	84	98	86	88	–
Islets pellet volume (ml)	4	4	4	4	3	2	3	4	4	6	2	3	4	2	–

Table 3. Univariate correlation analysis between the postpurification islet yield and the characteristics of the donors, of the pancreas and of the islet preparation. A linear regression was applied, the beta values correspond to the weight of the association between each variable and the postpurification islet yield. The 95% confidence interval is presented in the right column.

Variable	*P* (ANOVA)	Weight (Beta)	95% CI
Donor age	0.029	0.103	150 to 2744
Male gender	<0.001	0.181	34 048 to 103 000
Donor weight	<0.001	0.488	4154 to 5813
Donor height	<0.001	0.194	174 514 to 485 178
Donor BMI	<0.001	0.422	11 078 to 16 627
Trauma as cause of death	0.143	−0.069	−10 807 to 74 613
Cold ischaemia time	0.925	0.004	−4440 to 4888
Pancreas weight	<0.001	0.414	2259 to 3421
% of digested pancreas	0.001	0.154	919 to 3662
Pancreas digestion time	<0.001	−0.303	−14 250 to −7784
Presence of a major injury	0.008	−0.125	−237 400 to −35 615

additional technical difficulty, although obesity alone is not a risk factor for complications [11]. In the present work, increased rate of pancreas injuries was therefore not attributable to donor BMI. A higher donor weight, height, BMI and a high pancreas weight have been classically associated with better islet isolation outcomes [12–14]. Although a multivariate analysis of factor contributing to islet yield has not been performed (due to insufficient number of pancreata with major injuries), we can postulate that a statistical association with a low donor body weight would act as a confounding factor.

The rate of all pancreas injuries (minor and major) in our work was lower than the rate of pancreas injuries previously reported for whole pancreas transplant [7]. This is almost certainly because vascular injuries were not included in our analysis as they are not relevant and were not reported for pancreata procured for islet transplantation.

In whole pancreas transplantation, procurement injuries may result in pancreatitis, haemorrhage or thrombosis with clear and direct risk for the recipient. In contrast, the consequence of procurement injury may 'only' be to reduce the islet yield. This may not be readily apparent. Moreover, because the success rate of islet isolation in terms of resulting in a transplantable preparation may be less than 50%, even in experienced centres [15].

However, the procurement surgeon should be aware of the indirect consequences of severe injuries during pancreas procurement for islet transplantation.

The first consequence is financial: the average cost of each islet isolation in our centre is 9500 CAD (>8000 USD). Other European centres also reported a cost of 6000 Euros per isolation (>8000 USD) [16]. Based on the results of the present study, each centre should determine before starting islet isolation if the procedure is worthwhile depending on the aspect of the pancreas.

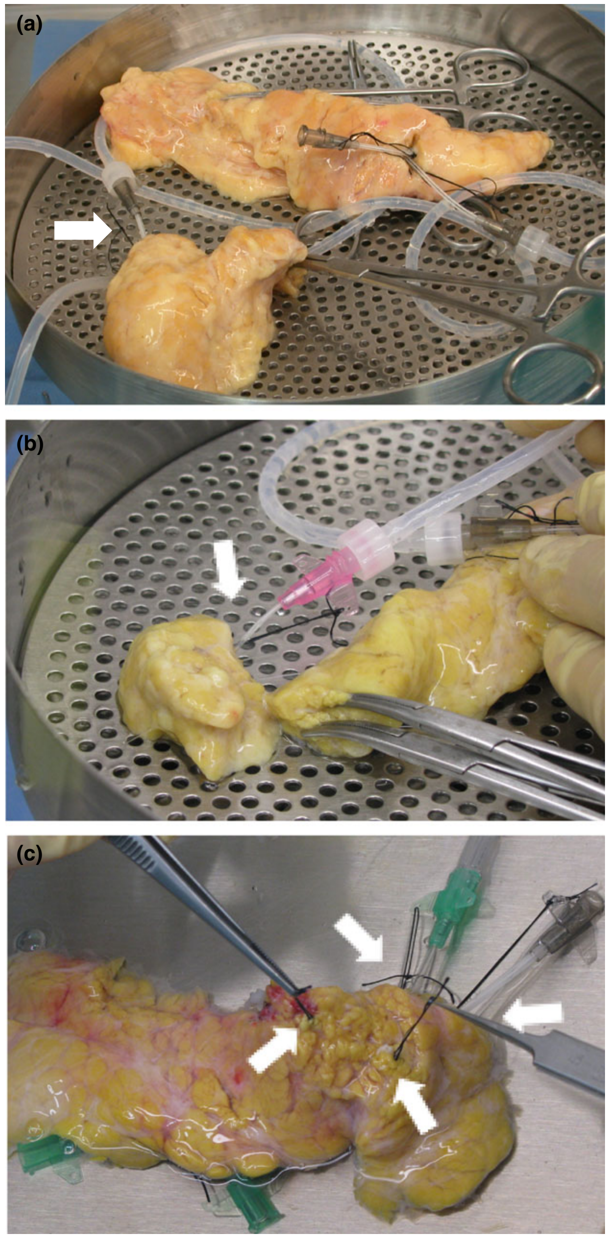

Figure 3 Attempts to repair the major injuries. To perfuse the injured parts of the pancreas disconnected from the main duct, additional catheters were inserted in completely amputated pancreas parts (a and b) or through opened duct stumps in case of longitudinal tears (c). Arrows show the presence of additional catheters and stitches to contain collagenase leaks.

The second consequence is the wasting of a pancreas in the context of organ shortage. Indications for islets transplantation include potentially life-threatening condition such as brittle diabetes with severe episodes of hypoglycaemia [17] that could jeopardize the health of a potential recipient. A loss of pancreas can therefore indirectly harm a potential recipient.

To prevent such injuries, we propose a simple guideline when procuring a pancreas for islet from a heart-beating donor. Those manoeuvres have already been described in a comprehensive textbook chapter dedicated to the surgical aspects of pancreas procurement for pancreatic islet transplantation [10]. We postulate that a preparation of a pancreas as for an whole organ transplant is not realistic because: (i) It is time-consuming, (ii) It requires an expertise that is not necessarily available among the procurement teams. Instead, we propose four simple manoeuvres during the warm phase of the procurement:

1. To open the omentum close to the great curvature of the stomach (requires several ligatures or sealing devices) or to open the gastro-colic ligament to give access to the anterior side of the pancreas. This manoeuvre should always be performed to assess the presence of an abnormality (tumour, etc.), to grossly evaluate the shape of the gland and to cool the organ during the cold phase.

2. To perform a complete Cattel–Braasch manoeuvre. The 'kocherization' of the duodenum and of the head of the pancreas will facilitate the dissection of the head of the pancreas during the cold phase, avoiding tears at this site.

3. To dissect the spleen from its posterior peritoneal attaches and to ligate the short gastric vessels to free the spleen from the great curvature of the stomach. This manoeuvre will permit to use the spleen as an handle during the dissection of the tail of the pancreas as for an organ procurement. However, an exsanguine isolation of the tail and body of the pancreas is not required at this point. The dissection of the spleen will permit to identify the tip of the tail of the pancreas during the cold phase, avoiding lesion at this site.

4. To identify the root of the mesenteric vessels below the uncinate process. A dissection beyond this point during the cold phase will avoid most of the lesions of the head/neck (representing most of the major and minor injuries). It is not important to dissect and to ligate the vessels at this site, as for an whole organ transplant, the vessels being afterwards discarded before the collagenase infusion.

The dissection of the upper pole of the head of the pancreas includes the skeletonization of the portal pedicle that is realized for the liver procurement and that should spare the pancreas.

In the presence of a documented major pancreatic transection injury recognized at the time the pancreas arrives in the islet isolation laboratory, we would recommend the following helpful manoeuvres to optimize pancreatic distension and islet yield: (i) Suture of capsular extravasation sites to minimize leak; (ii) Direct canulation of the exposed main pancreatic duct and both antegrade and retrograde distension where possible. We would avoid direct parenchymal injection without ductal canulation where possible, as this technique has rarely been helpful in our hands. In the presence of severe injury with uncontrolled leak, consideration should be given to discarding the pancreas for likely futility in islet isolation.

Conclusions

Although relatively infrequent, a major injury of a pancreas procured for islet isolation can compromise the islet yield and therefore the islet transplantation. We emphasize the importance of a careful dissection during the procurement, as none of the injuries observed were reported and probably had not been noticed in the present series.

Considering the lower islet yields after processing severely injured pancreata, we recommend assessing the quality of the pancreas in the islet isolation centre before starting the isolation procedure. Due to the limited number of pancreata with a major injury, we could not perform a multivariate analysis isolating the independent factors associated with a poor islet yield and their weight. We could therefore not build a predictive model integrating the major injuries, and until additional data are available we can only recommend caution when accepting such pancreata for islet isolation. Each centre should determine its own policy based on its financial resources and on the wait list.

We describe four easy manoeuvres during the warm phase of the procurement to decrease the rate of pancreas injuries.

Authorship

AA: writing of the manuscript, data analysis, design of study. TK: writing of the manuscript, data analysis, data gathering, design of the study. DO: data gathering, manuscript revision, design of the study. DB: manuscript revision, design of the study. NK: manuscript revision, design of the study. PS: manuscript revision, design of the study. AS: writing of the manuscript, data gathering, design of the study, supervision.

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