LETTER TO THE EDITORS

Evaluation of pancreatic duct cannulation methods for human islet isolation

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Dear Editors,

In this letter, we provide data for the first time on the comparison of two cannulation methods used in human islet isolation: single cannula method (SCM) versus dual cannula method (DCM). Islet Transplantation is an effective treatment for patients with refractory chronic pancreatitis (CP) and Type 1 Diabetes (T1D). Sufficient islets are required for achieving manageable metabolic status after transplantation. Collagenase infusion through the pancreatic duct is critical, as improper distention leads to poor yield [1].

Human islets were isolated from 14 research-grade pancreases, and 20 CP patients who underwent TPIAT at Virginia Commonwealth University. This study has been exempted by the institutional IRB. Islet isolation was performed using a modified Ricordi method [1–3]. In the SCM, the main pancreatic duct was cannulated from the pancreas head (Fig. S1a). Alternatively in DCM, the pancreas was transected at the neck using a scalpel and the pancreatic duct were cannulated, one toward the head and the other toward body-tail (Fig. S1b). The distension score was determined at the end of the enzyme perfusion by visual inspection of the pancreas size and firmness of the tissue by the technicians [1]; the assessment scores are described below (Table 1). Differences between groups were estimated using the Mann-Whitney *U*-test and a Student's *t* test. Categorical variables were compared using Chi-square and Fisher's exact tests.

Islet isolation results from research and TPIAT cases are summarized (Table 1). We observed an increase in the purity and decrease in the pellet volume in the high pure islets when DCM approach was used. Increased purity level suggests less exocrine contamination and hence the reduction in pellet volume in high purity islets. DCM may have caused better enzyme distribution to some parts of the pancreas resulting in improved purity and recovery of islets [4].

In TPIAT cases, the isolation outcomes were skewed because DCM was only adopted when SCM was not possible, due to blockage or closure of the duct caused by severe inflammation. Therefore, several parameters that resulted in significant differences may be attributed to disease condition and not due to cannulation technique.

Pancreatic ductal cannulation by SCM is technically challenging and in some TPIAT cases it is difficult to cannulate due to severe inflammation or anatomic variant such as pancreas divisum. If pancreatic duct is blocked due to inflammation or abnormal ductal anatomy, then the SCM cannot deliver collagenase to the pancreas effectively. Both SCM and DCM are widely used for cannulation, however, no studies evaluating the differences in isolation outcomes have been reported. Efficient and uniform delivery of enzyme to the entire pancreas is essential to achieve good isolation outcome. It is also well known that the tail region contains higher islet distribution compared to the head and body region [5]. It has been previously reported that the tail region often fail to distend well by SCM because distal ducts far from the catheter collapse due to rapid expansion of the tissue proximal to the catheter, causing leakage into interstitial space before reaching tail region [6]. In our study, no difference was seen in the distension quality between SCM and DCM in the research-grade pancreas. However, dual cannula method may improve enzyme delivery to the tail portion of pancreas, especially in some CP cases.

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Table 1. Islet isolation results between single cannula method (SCM) and dual cannula method (DCM).

Variables	Research-grade pancreas			TPAIT		
	SCM $n = 8$	DCM $n = 6$	*P*-value	SCM $n = 9$	DCM $n = 11$	*P*-value
Age (year)	39 ± 12	44 ± 14	0.6620	49 ± 12	49 ± 12	0.8964
Gender (male:female)	(2:6)	(3:3)	0.5804	(2:7)	(5:6)	0.3742
Body weight (kg)	89.3 ± 20.5	88.6 ± 18.8	0.9497	78.0 ± 16.2	72.4 ± 21.1	0.4561
Pancreas digestion						
Trimmed pancreas weight (g)	89 ± 16	99 ± 38	0.5474	100 ± 31	70 ± 33	**0.0496**
Percent of digest pancreas (%)	77.0 ± 9.2	74.8 ± 9.9	0.6743	84.4 ± 8.2	72.7 ± 15.8	0.0598
Distension score						
Head (% success for maximum distension)	3.9 ± 0.4 (87.5%)	3.5 ± 1.2 (83.3%)	0.4221	3.9 ± 0.3 (89%)	3.1 ± 1.1 (54.5%)	0.0576
Body & tail (% success for maximum distension)	3.8 ± 0.5 (75%)	4.0 ± 0.0 (100%)	0.2149	3.8 ± 0.4 (77.8%)	2.8 ± 1.3 (45.5%)	**0.0424**
Digestion time (min)	16 ± 3	17 ± 4	0.4702	16 ± 5	19 ± 6	0.2778
Dilution time (min)	37 ± 7	40 ± 5	0.1299	37 ± 5	31 ± 6	0.0556
Tissue volume postdigestion (ml)	36 ± 15	28 ± 9	0.2551	16 ± 12	9 ± 7	0.1048
Total islet yield postdigestion ($\times 10^3$ IEQ)	425 ± 123	398 ± 126	0.6904	502 ± 239	275 ± 217	**0.0394**
Islet yield per pancreas weight ($\times 10^3$ IEQ/g)	4.8 ± 1.3	4.3 ± 1.4	0.4900	5.1 ± 1.8	3.8 ± 3.1	0.2921
Percentage embedded islets	34.4 ± 4.9	31.4 ± 15.7	0.6226	23.3 ± 12.8	20.9 ± 14.3	0.6968
Final preparation						
Total islet yield ($\times 10e^3$ IEQ)	382 ± 177	433 ± 222	0.6398	499 ± 235	294 ± 244	0.0738
High	216 ± 128	166 ± 95	0.4338			
Middle	78 ± 31	150 ± 154	0.2166			
Low	82 ± 84	117 ± 58	0.3860			
Islet yield per pancreas weight ($\times 10^3$ IEQ/g)	4.1 ± 1.4	4.5 ± 1.7	0.7002	5.1 ± 1.8	4.0 ± 3.3	0.4201
Tissue volume (ml)	19 ± 8	22 ± 8	0.4415	14 ± 8	9 ± 7	0.2007
High	1.45 ± 0.5	0.8 ± 0.3	**0.0132**			
Middle	2 ± 1	4 ± 4	0.2179			
Low	16 ± 9	17 ± 7	0.7127			
Recovery rate (%)	88.4 ± 35.0	105.3 ± 25.2	0.3363			
Purity (%)	27 ± 14	17 ± 3	0.1168			
High	81 ± 7	89 ± 4	**0.0494**			
Middle	44 ± 3	48 ± 6	0.2370			
Low	15 ± 9	7 ± 3	0.0551			

IEQ, islet equivalent; TP-AIT, total pancreatectomy with islet autotransplantation.

Data expressed as mean ± standard deviation; statical significant results are highlighted in bold letters; distension assess score, excellent four point, very good three point, average two point, poor one point.

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Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The collagenase enzyme is injected via the cannulation of the main pancreatic duct.

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