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Coagulation abnormalities in deceased donors are associated with unsuccessful human islet cell isolation

Jong Man Kim [a], *Sang Man Jin* [b], *Seung Hoon Oh* [c], *Han-Sin Lee* [d], *Jae Hyeon Kim* [b,*], *Choon Hyuck David Kwon* [a], *Sung Joo Kim* [a,**], *Jae-Won Joh* [a], *Kwang Won Kim* [b]

[a] *Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Republic of Korea*
[b] *Division of Endocrinology and Metabolism, Department of Medicine Samsung Medical Center, Sungkyunkwan University School of Medicine, Republic of Korea*
[c] *Department of Medicine, Samsung Biomedical Research Institute, Republic of Korea*
[d] *Transplantation Research Center, Samsung Biomedical Research Institute, Republic of Korea*

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ABSTRACT

An equivalent islet number (EIN) greater than 300,000 is necessary for islet cell transplantation for a recipient who weighs about 60 kg. The aim of this study is to identify factors that affect isolation outcome. The most significant independent predictor for successful islet isolation from deceased donors was low international normalized ratio (INR).

1. Introduction

Islet transplantation has become a viable therapy for patients with type 1 diabetes mellitus [1]. However, more than one islet preparation is generally required per recipient to achieve insulin independence after transplantation. There is, therefore, an urgent need for more efficient processing to maximize islet cell recovery and quality. Previous studies have identified donor and isolation factors that affect the outcomes of islet isolation: in particular, high donor body mass index (BMI) and/or larger pancreas size are positively correlated with higher islet yields [2–4].

The purpose of the present study was to evaluate donor variables associated with the success of human islet isolation in a single processing center. We sought to define more stringent parameters for human donor pancreata and to optimize organ utilization for islet transplantation.

2. Methods

2.1. Pancreas procurement

Pancreata were obtained from heart-beating, multi-organ cadaveric donors after cerebral death and consent for islet

* *Corresponding author at*: Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, #50 Ilwon-Dong, Kangnam-Gu, Seoul 135-710, Republic of Korea. Tel.: +82 2 3410 1580; fax: +82 2 3410 0040.
** *Corresponding author at*: Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, #50 Ilwon-Dong, Kangnam-Gu, Seoul 135-710, Republic of Korea. Tel.: +82 2 3410 3476; fax: +82 2 3410 0040.
E-mail addresses: jaehyeonmd.kim@samsung.com (J.H. Kim), kmhyj111@skku.edu (S.J. Kim).
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transplantation was given by relatives. We retrospectively reviewed data collected from medical records and isolation records relative to pancreas processing for 10 donors from August 2010 to May 2011.

2.2. Islet isolation

Cold collagenase type P (Boehringer Mannheim, Mannheim, Germany) or Liberase HI (Roche Applied Science, Indianapolis, IN, USA) was injected through the pancreatic duct. The degree of distensibility was defined as follows: good, even distribution with little leakage of intraductal enzyme; moderate, uneven distribution with some leakage of intraductal enzyme; and poor, uneven distension with large leakage of intraductal enzyme, requiring additional enzyme injection into the parenchyma. We numbered each variable to describe the appearance of the pancreas using methods designed by the University of Pennsylvania. After trimming the peripancreatic fat tissue and vessels, pancreatic tissues were divided into 15–20 g masses and placed into Ricordi's isolation chamber for digestion. After completion of digestion, the islets were purified by separation on continuous gradients with Ficoll in a COBE 2991 cell processor (Cobe, Lakewood, CA, USA) or discontinuous gradients with Ficoll in tube centrifugation. An aliquot of islets was evaluated for equivalent islet number (EIN) under a scaled microscope using diphenylthiocarbazone (Sigma Chemical Co., St. Louis, MO, USA) staining. One EIN was defined as the islet tissue mass equivalent to a spherical islet of 150 μm in diameter. After purification, islet mass was calculated as the percentage of the total cell components under a microscope to measure purity.

2.3. Statistical analysis

Data are expressed as the median and range. Fisher's exact test was used for categorical variables and the non-parametric Mann–Whitney *U* test was used for continuous variables. The binary logistic regression model was analyzed and risk factors were considered significant if the *P* value to enter the model was less than 0.05. All *P* values represented were two-sided, with $P < 0.05$ indicating statistical significance. Registration and analysis of data were carried out using SPSS version 19.0 statistical software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Donor characteristics

We retrospectively reviewed the 10 pancreata accepted for islet transplantation. Islet isolations were deemed successful if they yielded adequate numbers of islets, defined as more than 300,000 EIN/pancreas. There were five adequate and five inadequate preparations. Table 1 summarizes donor variables

Table 1 – Donor characteristics.

	<300,000 EIN (*n* = 5)	>300,000 EIN (*n* = 5)	*P*-value
Gender			0.524
Male	4 (80%)	2 (40%)	
Female	1 (20%)	3 (60%)	
Cause of death			0.140
Cerebral infaction	0	1 (20%)	
Hypoxic brain damage	0	1 (20%)	
Internal cerebral hemorrhage	3 (60%)	0	
Myocardial infarction	0	1 (20%)	
Subarachnoid hemorrhage	1 (20%)	1 (20%)	
Subdural hemorrhage	1 (20%)	1 (20%)	
Cardiopulmonary resuscitation	2 (40%)	2 (40%)	1.000
Brain operation history	2 (40%)	2 (40%)	1.000
History of hypertension	0 (0%)	1 (20%)	0.221
Smoking history	2 (40%)	4 (80%)	0.524
Alcohol history	3 (60%)	3 (60%)	1.000
Continuous renal replacement therapy	1 (20%)	0 (0%)	0.221
Age (years)	41 (39–75)	43 (21–51)	0.465
Body mass index	24.4 (17.3–32.2)	21.8 (19.5–25.0)	0.602
Intensive care unit stay (days)	5 (2–8)	7 (3–11)	0.458
Mean blood pressure (mmHg)	78.3 (70.7–82.0)	80.0 (71.3–105.0)	0.456
White blood cells (/μL)	18,380 (9500–25,110)	16,500 (8550–24,910)	0.754
Hemoglobin (g/dL)	10.7 (8.8–12.1)	9.2 (7.0–14.6)	0.347
Platelet (/μL)	60,000 (24,000–470,000)	89,000 (85,000–387,000)	0.117
INR	1.50 (1.38–2.09)	1.28 (1.03–1.35)	0.009
Serum sodium (mequiv./L)	144 (128–165)	149 (129–154)	0.754
Serum creatinine (mg/dL)	1.4 (1.0–5.6)	0.8 (0.6–1.3)	0.028
Glucose (mg/dL)	144 (115–210)	200 (101–276)	0.347
Amylase (IU/L)	142 (116–240)	109 (38–250)	0.602
Lipase (IU/L)	18 (15–76)	25 (14–398)	0.917
AST (IU/L)	66 (59–214)	27 (23–61)	0.042
ALT (IU/L)	35 (34–97)	31 (20–39)	0.146
Total bilirubin (mg/dL)	1.4 (1–5)	0.6 (0.5–1.0)	0.157