



LARGE SCALE ISOPYCNIC ISLET PURIFICATION UTILIZING NON-TOXIC, ENDOTOXIN-FREE MEDIA FACILITATES IMMEDIATE SINGLE-DONOR PIG ISLET ALLOGRAFT FUNCTION

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Abstract 120

Early graft function has been difficult to accomplish in clinical islet allotransplantation. It is becoming apparent that reagents used for islet preparation may stimulate the inflammatory response to islet grafts and may thereby interfere with early islet function and engraftment. The purpose of this study therefore was to develop islet purification density gradient media restricted to non-toxic, endotoxin-tested components and to subsequently test whether islets purified on the refined gradients immediately reverse diabetes in the relevant preclinical single-donor pig allograft model.

Density gradients were constructed based on iodixanol x-ray contrast media and UW solution which are both approved for clinical use. In the first set of experiments, the osmolality most suitable for islet separation was identified. The effect of four different osmolalities (320; 350; 375; and 400 mosm/kg) on the density profile of islet and acinar tissue was studied by means of continuous test gradients. In the second part of the study, iodixanol/UW gradients were applied for large scale continuous islet density gradient purification on a Cobe 2991 and the percentage recovery of islet equivalents (IE) in fractions with purities $\geq 90\%$ from iodixanol/UW was compared to Ficoll Na-diatrizoate gradients (previous standard). To test whether iodixanol/UW gradients interfere with immediate reversal of hyperglycemia posttransplant, 7134 \pm 1830 purified IE/kg body weight were intraportally transplanted into five streptozotocin-diabetic pigs. The percentage of exocrine tissue contaminating 95% yield of islets were 0.45 \pm 0.96%, 0.0 \pm 0.0%, 0.45 \pm 0.69%, and 0.80 \pm 1.00% for 320, 350, 375, and 400 mosm/kg iodixanol/UW gradients, respectively. The percentage recovery of pure islet equivalents from 350 mosm/kg iodixanol/UW (n=6) gradients was significantly higher compared to the standard Ficoll Na-diatrizoate (n=4) gradient (86.2 \pm 11.8% vs 67.0 \pm 9.3%; p=0.013).

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LARGE SCALE ISOPYCNIC ISL...

Four out of five consecutive diabetic single-donor pig islet allograft recipients became normoglycemic and insulin-independent within 24 hrs following transplantation.

The data indicate that single donor pig islet allografts purified on non-toxic, endotoxin-free gradients establish insulin independence immediately. Osmolality adjustments should make iodixanol/UW gradients also suitable for human islet purification. Failure to achieve immediate insulin independence in the clinical setting would then point to non-technical obstacles.

Section Description

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