Early results and technical aspects of endoscopic islets autotransplantation in a patient with contraindication to transplantation into the portal vein

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ABSTRACT

Chronic pancreatitis (CP) is a severe illness, which may cause significant deterioration of patients’ quality of life because of constant pain. Pancreatic resection followed by pancreatic islets autotransplantation might be a successful therapeutic option for a selected group of patients. Successful islets transplantation into gastric sub-mucosa in a pre-clinical study on pigs makes gastric submucosa a promising option for future. **Aim of this paper was to report a successful resection of the pancreas and endoscopic islets autotransplantation into gastric sub-mucosa in man. Patient and methods.** A 53-year old man with alcohol-related chronic pancreatitis for 15 years was operated on. Patient underwent pancreatectomy. Endoscopic gastric sub-mucosa
INTRODUCTION

Islets transplantation has become a very useful method of managing problems with brittle diabetes (1) and painful chronic pancreatitis (2). Since 1999 only in Europe more than 20 new centres, which procure and perform isolations have been established. Since then, according to Berney, procedure volume in Europe has been twice as large as in the US and reached almost 1400 islets transplantations in 775 patients (3). Growing interest in islets transplantation uncovered toward new possible problems that could be solved with that method. In US, the patients with chronic pancreatitis, who have undergone pancreatectomy and islets autotransplantation, have become a substantial part of activity of almost all transplant centres (2). Autotransplantation of islets in chronic pancreatitis gives hope for cure and improvement of quality of life in many patients. Diabetes which develops after pancreatocmy is a serious problem because it may cause a severe hypoglycaemia which may lead to death in up to 50% of those patients (4). If islets are isolated from the resected pancreas and transplanted back to patients, they may prevent brittle episodes, even if sometimes the procedure does not lead to full insulin independence. Full pancreatectomy, performed in order to proceed with islets isolation, may prevent the development of pancreatic cancer (5) that might develop along with chronic inflammation of the pancreas. Pancreatitis, and chronic pancreatitis is mainly caused by biliary stones or excessive alcohol intake (6). Unfortunately, excessive alcohol intake may lead to liver problems such as liver cirrhosis and portal vein thrombosis which may lead to portal hypertension. Portal hypertension can make islets transplantation into the portal vein risky or even impossible. In those patients alternative implantation sites should be considered. For the last ten years many alternative implantation sites have been analysed, both in preclinical and clinical models (7-17). Gastric submucosa seems to be an attractive site for transplantation due to good perfusion (8), easy endoscopic access and the most physiological insulin outflow to portal vein.

The aim of this paper is to report technical aspects and results of endoscopic islets autotransplantation into gastric submucosa in man.

METHODS

A 53-year old man with alcohol related chronic pancreatitis for 15 years was operated. Past medical history: 3 months earlier patient was diagnosed with type 2 diabetes - only dietary treatment was introduced. Patient was suffering from chronic pain, which was treated with opioid analgesics. 15 years earlier patient had been operated on due to peptic ulcer perforation, which was sutured. In laboratory testing anti-HBc, anti-HBe was detected – the patient must have undergone hepatitis. CT scans showed right portal vein thrombosis (Pic. 1). Patient was offered pancreatectomy and splenectomy modo Child with experimental endoscopic islets transplantation into the gastric submucosa. Levels of fasting c-peptide were measured prior to procedure and at 1,2,3,4,5,7,14,30, 90 and 180 days post autotransplantation. C-peptide stimulation (CPS) test was performed prior to procedure and one, three and six months post autotransplantation. Fasting glycaemia and oral glucose tolerance test (OGTT) was performed prior to and at 7, 30, 90 and 180 days post transplantation. Control gastroscopy and endoultrasonography (EUS) were performed within first week and then at three and six months post-transplantation.

RESULTS

Surgical procedure. The patient underwent Child pancreatectomy with splenectomy and endoscopic islets transplantation into gastric submucosa. Pancreas was resected with splenic artery and vein. After retrieval, pancreas was immediately flushed with 1000 ml of UW solution through splenic artery and vein and transferred for isolation.

Isolation procedure. Before isolation the pancreas was stored for one hour in simple hypothermia. Only part of the head, corpus and the tail of the pancreas with the mass of 34 g were used to isolation. Pancreas was digested in a solution of collagenase and protease in a total volume of 150 ml Perfusion Solution (Mediatech Cellgro). The pancreas was heavily fibrotic, after injection reached mass of 49 g. Dilution process was started after 10 minutes after digestion using 4 liters of Dilution Solution (Mediatech Cellgro) supplemented with 20% human serum albumin (HSA) and the Pen/Strep mixture. The centrifugation (1200 rpm) gave a total volume of 6 ml of the washed pellet,

Isolation: 264 000 IEQ were isolated. Pellets had 6 ml and were suspended in 60 ml of Ringer’s solution. Patient did not require any insulin or hypoglycemics post surgery. Pre-procedure fasting C-peptide was 0.89 ng/ml. Post-procedure C-peptide was between 0.44 and 1.36 ng/ml. Conclusion. Preliminary results of endoscopic gastric sub-mucosa islets autotransplantation indicate that it might be an alternative site for islets autotransplantation in case of patients with contraindication for transplantation into the portal vein.
which was suspended twice in CMRL1066 supplemented with 20% HSA and antibiotics, and then supernatant was centrifuged. Estimated number of islets was 264,000 IEQ, resulting in 3770 IEQ per kg of body weight of the recipient. The final product was suspended in 60 ml of Ringer’s Solution. The endotoxin was determined (2 EU per kg of body weight of the recipient) and the microbiological cultures were obtained. Direct Gram staining of final product was evaluated.

**Transplantation procedure.** Gastroscopy was performed under general anaesthesia. No lesions within gastric wall were observed. 18 injections were performed and 3 to 5 ml of pancreatic islets suspension was introduced into the submucosa of gastric corpus and fundus. No complications were observed during the procedure (Video 1).

**Post-operative period.** Patient received insulin intravenously and glucose for 72 hours as a “background” but after that – Patient did not require any insulin nor oral hypoglycemics. In the early post-operative period, the patient suffered from pneumonia and pulmonary embolism successfully treated with antibiotics and low molecular weight heparin. Post-procedure gastroscopies (7 days; 3 and 6 months) did not reveal any signs of inflammation or ulceration. EUS did not reveal any fluid collections within the gastric wall.

**Metabolic results.** Fasting C-peptide prior to procedure and up to six months post procedure were similar (Fig.1). Stimulated C-peptide prior to transplantation reached 9.63 ng/ml, while the highest concentration after resection and transplantation was 5.22 ng/ml (Fig.2). Oral glucose tolerance test performed prior to procedure and up to six months post-transplantation reached 243 mg/dl (Fig.3).

**CONCLUSION**

Preliminary results of endoscopic gastric submucosa islets autotransplantation indicate that it might be an alternative site for islets autotransplantation in case of patients with contraindications for transplantation into the portal vein.

**DISCUSSION**

To the best of our knowledge, it is the first case of endoscopic islets autotransplantation in man. After several publications showing encouraging results of autotransplantation (8) and allotransplantation in pigs (18, 19), it was deemed safe to implement the technique in man. Possible complications had previously been described in large animals. Application of this technique should be restricted to patients with contraindications to transplantation into the portal vein. Although sub-mucosal space gives a hope for avoiding instant blood-mediated inflammatory reaction, which is present if islets are transplanted into the portal vein, nevertheless, so far we have only preliminary results from one patient. Further analysis should be performed starting with autotransplantation and further allotransplantation.
BIBLIOGRAPHY


