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Insulin Independence Achieved After Islet Transplantation Through an Indwelling Catheter in the Umbilical Vein

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Abstract

Introduction: **The liver is the primary target location for islet infusion and portal vein catheterization is generally used.**
Background: **Current islet infusion approach via portal vein of liver has various defects. The aim of this work is to investigate the feasibility and safety of an indwelling catheter in the umbilical vein for intra-portal islet transplantation**
Patients and methods: **Twelve patients with type 1 diabetes mellitus were generally anesthetized and incised in the middle-right of upper abdomen. The umbilical vein was identified, dissected and catheterized. The catheter was located in trunk of portal vein, and the islet suspension was infused. After surgery the catheter was secured to skin for optional subsequent infusions and flushed with heparinized saline once per day within one month post-operation. The catheter was removed after one month post-operation. The therapeutic effects and peri-operation complications were observed.**
Results: **All patients successfully underwent catheterization and transplantation. Insulin independence was finally achieved in 75% (9/12) patients at 1 year post-operation; seven patients received a second infusion. The mean surgical duration was 58.5±10.3 minutes, the mean incision length was 7.6 ± 0.9 cm, and the estimated hemorrhage volume was 52.5±13.6 mL. No significant change in portal pressure was observed (before infusion 3.8±2.0 cm H_2O, after infusion 3.4±1.9 cm H_2O, $p>0.05$). Neither infection nor severe hemorrhage was found after surgery.**
Discussion: **The umbilical vein approach is easy to conduct and avoids digestive side effects, allowing a second islet infusion through the indwelling catheter.**
Conclusions: **It is feasible, convenient, and safe to use an indwelling catheter in the umbilical vein for islet transplantation.**

Keywords: Portal vein, Umbilical vein, Islet transplantation, Diabetes mellitus.

Introduction

Islet transplantation is one of the effective and promising options for type 1 diabetes mellitus treatment[1-4]. The liver is the primary target location for infusion and portal vein catheterization is generally used. Percutaneous transjugular, percutaneous transhepatic, laparoscopically transmesenteric and laparoscopically transumbilical approaches were often utilized to access the portal[5-10].

Background

Current islet infusion approach via portal vein of liver has various defects. Percutaneous trans-hepatic puncture is risk of possible severe hemorrhage and portal thrombosis. The laparoscopic entry techniques require longer surgical duration and have an increased rate of catheterization failure. Moreover, the catheters were not allowed to indwell for subsequent infusions.

In the current study, we performed open surgery, catheterized the umbilical vein and infused islets into the portal vein. The catheter was indwelled for one month after surgery. Therapeutic effects, surgical parameters and complications were observed and analyzed to evaluate feasibility and safety.

Patients and Methods

Patients

Twelve type 1 diabetic patients underwent islet transplantation (islet transplantation alone, ITA, n = 4; simultaneous islet and kidney transplantation, SIK, n = 8) between June 2008 and December 2012. The patients' mean age was 29.9 years (range from 21 to 37 years, male = 9 and female = 6) and average history was 9.6 (3-16) years. Approval of the Ethics Committee and informed consent of the patients were obtained.

Islet preparation

Islets were isolated from the pancreas obtained from deceased multi-organ donors[2]. Briefly, the pancreas was recovered from brain-dead donors after they had been pronounced brain dead. The pancreatic duct was perfused with a cold enzyme for human islet separation (Liberase; Roche Diagnostics, Indianapolis, IN, USA). The pancreas was enzymatically and mechanically dissociated before the islets were separated on a refrigerated Cobe 2991 centrifuge (Cobe BCT, Lakewood, CO, USA). Purification was performed by centrifugation on continuous Ficoll gradients (Seromed-Biochrom, Berlin, Germany). Islets were cultured in CMRL1066 medium (Mediatech-Cellgro, Manassas, VA, USA) supplemented with 0.5% human serum albumin and incubated at 37°C in 5% CO_2 and 95% humidified air for 12 to 24 h. Islet numbers were quantified in duplicate with the use of an islet standard diameter of 150 μm and islets were tested for sterility, endotoxin, and mycoplasma.

Surgical protocol for umbilical vein catheterization.

A 7 cm incision was made in the middle-right of upper abdominal under general anesthesia. The umbilical vein was identified located 4 cm beyond umbilicus, which was then half dissected transversely and the atresic venous lumen was recanalized with a common duct probe (3 mm-5 mm, BAKES). A breakthrough feeling would be sensed after approaching forward for 10-14 cm and the umbilical vein was successfully recanalized. The common duct probe was pulled out. A catheter (single lumen central venous catheter, 16-20G, TUOREN, China) was then cannulated for 15 cm into left branch of portal vein through umbilical vein. The procedure was observed with Doppler ultrasound (LOGIQ S6, GE). Patency of catheter was confirmed by smooth infusion of heparinized saline and withdrawal of blood. Portal pressure was measured by the pressure sensor of monitor. Fingertip blood glucose was measured. Islet preparation (100 ml) was infused by gravity, and then the containing bag was flushed twice with 50 ml 1066 culture solution (Sigma). Islet equivalent quantity and infusion duration was documented. Portal pressure and fingertip blood glucose were measured again after infusion. The umbilical vein was securely ligated with the catheter indwelling, secured to upper end of the incision. The peritoneum was closed, and subcutaneous tissue and skin were approximated, respectively.

Post-operative management

The exogenous insulin injection was continued and decreased according to blood glucose monitoring records. Subcutaneous injection of 2500 IU low molecular weight heparin (Fragmin; Pfizer, New York, NY, USA) twice per day for 2 weeks and 50 mg Etanercept (Immunex) once per week for 4 weeks was given to alleviate portal thrombosis and immediate blood-mediated inflammatory reaction. Intravenous antibiotics (Cefazolin, 2 g, twice a day; Langchem, Shanghai, China) and oral ones (Bactrim, 2 tablets, twice per day, AR Scientific, Philadelphia, PA, USA) were administered for the first week and the subsequent 3 weeks, respectively. The catheter was flushed with heparinized saline once per day for 1 month to prevent obstruction of the catheter by thrombosis. The catheter was removed after 1 month, and the local was pressed for 15 minutes. The steroid-free immunosuppressive regimen consisted of low dose tacrolimus (Prograf; Fujisawa, Munich, Germany), sirolimus (Rapamune; Wyeth, Madison, NJ, USA), mycophenolate mofetil (Cellcept; Roche, Basel, Switzerland), and alemtuzumab induction therapy (Campath-1H; Millennium Pharmaceuticals, Cambridge, MA, USA).

Management of re-transplantation

After 2 weeks, patients with exogenous insulin reduction <80% were scheduled for subsequent islet infusions. The infusion should be performed within one month, before removal of the catheter.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Paired *t* test was used to compare results within groups.

Results

All patients successfully underwent catheterization and transplantation. Among the 12 patients, 7 received a second infusion (all using indwelling catheters), and 75% (9/12) were independent of exogenous insulin at 1 year post-operation. The quantities of infused islets

were 13536.2±3653.6 equivalents/kg body weight. The pre-operative insulin dosage was 43.4±7.1 units. The dosages of the 3 insulin-dependent patients reduced to 30.8% (12/39), 47.6% (20/42) and 64.3% (27/42) at 1 year, respectively. One rejection episode was observed at two weeks in one patient. He lost the insulin independence and the exogenous insulin requirements returned to 47.6% (20/42). Although immunosuppressive drug dose was increased immediately, the rejection consequence was not fully reversed.

The mean surgical duration was 58.5±10.3 minutes. The incision length was 7.6±0.9 cm and the estimated hemorrhage volume was 52.5±13.6 mL. The catheter location in the left branch was successfully confirmed and the procedure of islet infusion into the portal vein was monitored with Doppler ultrasound (Figure 1). No significant change in portal pressure was observed before and after the infusion (before: 3.8±2.0 H_2O, after: 3.4±1.9 cm H_2O, $p>0.05$).

No complications such as infection or severe hemorrhage were observed after surgery. The patients were adequately counseled to maintain the catheter in position. No catheter slipped out or was removed unexpectedly. The catheters were safely removed out from all patients at one month, without severe hemorrhage or seroma after local pressing. This was confirmed by ultrasound.

Discussion

Percutaneous transhepatic approach is generally utilized at most islet centers, which is convenient and micro-invasive. It risks post-operative hemorrhage and transfusion is required in severe conditions[1]. Biological adhesive is used to patch puncture point, it also may result in portal embolism if the adhesive detaches. Shapiro et al. reported two cases of transfusion in 15 patients who underwent islet transplant using percutaneous transhepatic method[1] and complications such as hemathorax and hemoperitoneum[11].

Transjugular intrahepatic portal vein catheterization was also reported for islet infusion, which reduced the risk of hemorrhage. However, it is more technically complicated and time-consuming[10].

Intar-portal infusion through catheter in the mesenteric vein and the umbilical vein using laparoscopy was reported by Osama Gaber A and Movahedi, respectively[7,9]. The risk of hemorrhage was low, whereas high catheterization success rate was not readily achieved and it was inconvenient to leave the catheter indwelled for multiple infusions.

In the current study, we investigated umbilical vein catheterization with open surgery for intra-portal islet infusion. The umbilical vein is a channel between the fetal and the maternal, one end of which is connected to the placenta while the other connected to the portal vein. The umbilical vein gradually closes but the potential lumen still remains covered with epithelium. It may be re-canalized by fluid pressure or manual dilatation[12]. In the current study, all umbilical veins were successfully re-canalized. The umbilical vein is a tributary of left portal branch and the infused islet accordingly enters the liver section that it feeds. This characteristic may be beneficial that the adverse effects such as infection or tumorigenesis will be localized and remedy managements be facilitated.

In the study, the open surgery had only slightly bigger lesion than that of laparoscopy, but had remarkable shorter operation duration. The umbilical vein approach avoids handling of the stomach or intestines, minimizing the risk of digestive side effects. Patients can undergo a second islet infusion through the indwelling catheter. The infusion procedure is very convenient without a surgery or anesthesia, which is unachievable by percutaneous portal puncture or laparoscopic surgery. Aside from islet infusion, the umbilical vein catheter is also ready for intrahepatic medication such as the anti-inflammatory agent Etanercept or pentoxifylline[7].

Conclusions

Islet transplantation through an indwelling catheter in the umbilical vein is convenient, feasible and safe.

Declaration

The authors of this manuscript have no conflicts of interest to disclose.

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