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Babak Movahedi
Bart Keymeulen
Mary-Helen Lauwers
Eva Goes
Nadine Cools
Georges Delvaux

Laparoscopic approach for human islet transplantation into a defined liver segment in type-1 diabetic patients

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B. Movahedi · B. Keymeulen
M.-H. Lauwers · E. Goes · N. Cools
G. Delvaux (✉)
Department of Surgery,
Vrije Universiteit Brussel,
Laarbeeklaan 101, 1090, Brussels, Belgium
E-mail: georges.delvaux@az.vub.ac.be
Tel.: +32-2-4774515

Abstract Intra-portal islet transplantation is usually performed by cannulation of a mesenteric vein during laparotomy or through percutaneous trans-hepatic cannulation of a portal branch. In this study, we describe a new laparoscopic technique for intra-portal islet transplantation in a defined liver segment, as an alternative to the current procedures. Eighteen type-1 diabetic patients underwent laparoscopic re-permeabilisation of the umbilical vein, followed by catheterization of the left branch of the portal vein. The catheter was guided under fluoroscopic control into a chosen liver segment. It was then secured to the skin or connected to an implantable venous access device. Thereafter, the islet preparation was slowly injected. There was no rise in portal pressure. The median duration of the procedure was 85 min. The procedure was successful in 17 of 18 cases. There were no surgical complications. We conclude that this laparoscopic procedure is a feasible, convenient, and safe alternative method of islet transplantation. Moreover, it allows multiple deliveries of islets into the same liver segment.

Keywords Diabetes mellitus · Intra-portal islet transplantation · Laparoscopy · Umbilical vein · Implantable venous access device

Introduction

Diabetes mellitus is a common disease with high morbidity and mortality. At the end of the 20th century, an estimated 124 million people worldwide suffered from this disease [1]. Intensive therapy delays the onset and slows the progression of diabetic secondary complications, however, to date they cannot be prevented completely [18]. Islet cell transplantation, as a new therapy and potential cure for type-1 diabetes, has been investigated in selected patient groups [10, 14].

Intra-portal transplantation, in which donor islet cells are injected into the portal venous network, has been studied most thoroughly. After intra-portal injection, islet cells are incorporated in the portal spaces. There, they are surrounded by normal liver tissue [13, 16], and come in direct contact with portal blood and its glucose content. All patients in the well-documented cases of insulin independence following transplantation received intra-portal islets [4].

The portal vein can easily be accessed during a combined liver–islet transplantation, or a simultaneous islet and kidney transplantation. In such cases, a catheter is guided to the intra-hepatic portal veins via cannulation of a mesenteric vein, and left in place for subsequent islet infusion [13]. In addition, percutaneous trans-hepatic catheterization of the portal vein has recently become a preferred method. However, this procedure can cause major complications [2, 8, 12, 17]. A third way of reaching the portal vein is by re-permeabilisation of the umbilical vein in the ligamentum teres hepatis. However, this requires a midline laparotomy, which makes it less desirable, unless the islet transplantation is done simultaneously with a liver or kidney transplantation.

Catheterization of the left branch of the portal vein, through the ligamentum teres, was described more than 30 years ago [5]. It required extra-peritoneal dissection of the umbilical end of the ligamentum teres under general or local anaesthesia, to then catheterize the portal vein. The procedure's success rate was approximately 80%. Initially, this technique was commonly used for haemodynamic studies of the portal blood flow and for direct portography. It has now been abandoned in favour of other investigational methods to study portal haemodynamics.

In the present study, we adapted the old trans-ligamentary approach. Laparoscopic catheterization of the ligamentum teres allowed us to access the portal veins and to transplant the islet cells into a well-defined liver segment. This method proved to be an easy and safe way to reach the portal bloodstream.

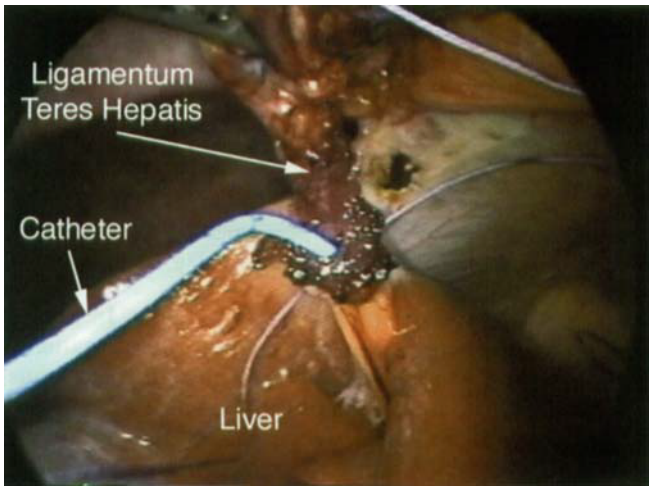

Fig. 1 Laparoscopic view during the procedure. The catheter is inserted through the re-permeabilised umbilical vein and firmly tied to the ligament once the correct position is obtained

Materials and methods

Patients

Twelve men and six women with insulin-dependent diabetes (C-peptide levels < 0.02 nmol/l) were selected for human pancreatic islet transplantation. Their mean age was 43 (range 29–56) years. All recipients had previously undergone renal allograft transplantation for renal failure (mean time 4 years, range 2.3–5.5 years).

This study is part of a European Union programme on beta-cell transplantation in diabetes. It has been approved by the ethical committees of university hospitals participating in patient recruitment and transplantation. All participants gave their informed consent. The final results on the first seven patients with intra-portal transplantation of purified and functionally standardised beta-cell grafts have been published previously [10].

Operating procedure

The procedure was performed under general anaesthesia. Three trocars were used, after the pneumoperitoneum had been established: one 10-mm infra-umbilical trocar, and two 5-mm trocars in the right and left flanks. A laparoscope with a visual angle of 25° was used. The round ligament, which appears as a white firm string, was dissected from its free border at a distance of approximately 2 cm from the liver. A transverse incision of the ligament was made with scissors, and a catheter with a soft guide wire was inserted into the virtual lumen of the umbilical vein and gently pushed up to the left branch of the portal vein inside the liver (Fig. 1). Resistance was usually felt at this level; it was easily overcome by gentle pressure. After the guide wire had been withdrawn, blood flow confirmed that the portal vein was accessed. A portal branch leading to a liver segment in the left or right lobe of the liver was then selected under fluoroscopic control. A small amount of iodine-based contrast fluid was used to check the proper position of the catheter tip in the segmental branch of the portal vein (Fig. 2). The catheter was tied closely to the ligament. Finally, the catheter was secured with two stitches onto the skin. Saline (1,000 ml with 5000 U heparin) was continuously perfused through the catheter until the endocrine cell suspension could be injected.

After 6 to 24 h, the position of the catheter was checked by ultrasonography. Then, the islet-cell preparation was injected over 20 min, followed by local infusion of 5,000 U of heparin in 1 l of saline over 24 h. The method of islet isolation and culture has been described previously [10]. The intra-portal pressures were measured, through a catheter connected to a transducer, before and after the injection of the cells.

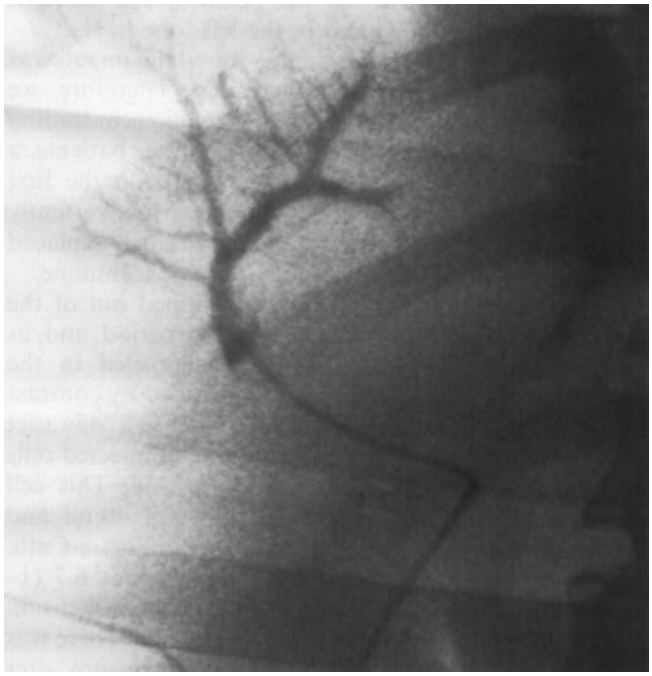

Fig. 2 The correct positioning of the catheter is achieved by fluoroscopy. In this case the catheterized portal branch supplies segment 7 of the liver

In five of the 18 patients, the intra-portal catheter was connected with an implantable venous access device (Port-A-Cath Low Profile Venous System, SIMS Deltec, St Paul, USA). This reservoir was implanted subcutaneously at the right costal margin. In these patients, the intra-hepatic catheter was fixed to the round ligament with a double loop. The access device was flushed with diluted

heparin prior to and then every 2 weeks after its use for islet transplantation. It was removed under local anaesthesia as soon as the last graft was given.

Patient follow up after transplantation included monitoring of liver, kidney and bone marrow functions. Ultrasonography and MRI of the liver were performed prior to and soon after transplantation and during a follow up period of at least 36 weeks. The survival of the graft was assessed by C-peptide assay.

Results

This technique was performed on 18 patients. In five of them, a Port-a-Cath system was used. Three patients had a second injection of islet cells through the venous access device. The median operating time for all patients was 85 min (40–330 min). Once we had undergone a learning curve of five patients, our operating time did not exceed 120 min, with a mean of 80 min in the last 13 patients. In all cases but one, the umbilical vein could be re-permeabilised easily, and the catheter positioned adequately. The catheter had a tendency to slide more easily towards the right liver lobe than towards the left lobe. As a result, the catheter was positioned in the right liver lobe in 12 patients, and in the left lobe in six.

In one of the 18 patients, the round ligament was atrophic and could not be catheterized. Therefore, we used a mini-laparotomy to cannulate a colic vein leading to the portal axis in this patient. In two other patients, a displacement of the catheter occurred within the first hours after the procedure. One patient inadvertently avulsed the catheter while awakening. We easily replaced the catheter by using the same laparoscopic technique.

In the other patient, the catheter slipped out of the portal vein unnoticed during the recovery period, and, as a consequence, the islet cells were deposited in the peritoneal cavity. This failure was confirmed by contrast injection. The patients received $2{,}676 \pm 1{,}245$ islet equivalents/kg body weight. The volume of injected cells was between 550 and 1,960 (mean: 993) µl. This cell mass was suspended in a total volume of 40 ml and slowly injected through the catheter or the Port-a-Cath.

The mean (range) intra-portal pressure was 6.7 (1–14) mmHg) prior to the injection of the cell suspension and 6.7 (2–13) mmHg immediately thereafter. There was no significant change in the intra-portal pressure after the islet injection (mean: 0 mmHg, range: –2 to 3 mm Hg). Patients who had received their venous access device some days prior to the graft injection could leave the hospital 1 day after the procedure. The device was removed after the last islet injection. All patients were followed-up for their islet grafts for at least 36 weeks, and thereafter, for as long as the graft was functional. No surgical or infectious complications were reported after the procedure or during the follow-up.

Four patients still have graft function, 7, 6, 5 and 4 years after the last injection, respectively. Two of them received a venous access device. One had a second implant. In three out of four patients with sustained graft function, a localised zone of slight steatosis was detectable on MRI images, starting from 2 to 12 months post-implantation. Steatotic changes were confirmed by a liver biopsy in one patient. The steatotic zones were sharply limited to the liver segments primarily used to harbour the graft. In one patient, the diagnosis of an oat cell carcinoma of the lung was made 19 months after transplantation. The patient died 6 weeks later.

Discussion

A total of 394 human pancreatic islet allografts has been reported between 1990 and 31 December 2000 [4]. The intra-hepatic portal system was the most commonly used implantation site [21]. Most procedures were performed at the time of the transplantation of another organ or as an islet transplantation following kidney transplantation (islet after kidney) [4]. Therefore, the established technique for islet transplantation was a midline laparotomy, whereby access to the portal tract was gained by cannulation of the middle colic vein or by catheterization of the round ligament [16, 19].

The ligamentum teres hepatis (the round ligament) represents the remnant of the umbilical vein. The latter collapses from the flattening and the narrowing of the lumen immediately after birth. At the internal part of the ligamentum, the collapse is caused by the elastic properties of the vessel and not through thrombosis and subsequent organisation [3]. Therefore, patency of the umbilical vein can usually be restored by dissection and by slipping a probe or a catheter into the virtual lumen of the ligament.

Re-permeabilisation of the umbilical vein for islet transplantation has been described previously by Scharp et al. They used a midline abdominal incision to reach the round ligament [15]. The use of laparoscopy in human islet transplantation is rare. We found a single report where laparoscopy was used to implant the islets between the two layers of peritoneum [9]. In the present study, we catheterised the umbilical vein by using a laparoscopic approach. We successfully cannulated the umbilical vein in 17 of 18 cases (94.4%). Unlike a mini-laparotomy, laparoscopy offers one the possibility of performing a dissection of the round ligament close to the margin of the liver and the portal vein, thus minimising the risk of a perforation during the introduction of the catheter. Furthermore, an abdominal incision is prevented. This reduces the morbidity related to a laparotomy and improves the cosmetic results.

In one patient, atrophy of the pars umbilicus of the left branch of the portal vein prevented access, and a laparotomy was required. Since that event, pre-operative ultrasonography of the liver has been used to confirm the normal anatomy and patency of the portal system

prior to the laparoscopic procedure. After we had passed the learning curve with the first five patients, our operating time for the laparoscopic procedure was comparable to that needed for the portal system to be reached by an abdominal incision.

In recent years, percutaneous trans-hepatic catheterization of the portal vein has been frequently used for islet transplantation. In this approach, the portal vein is catheterized under CT or ultrasound and fluoroscopic control [20]. Before the era of islet transplantation, the percutaneous technique was mainly used for diagnostic purposes. This procedure is performed under local anaesthesia and sedation, in a relatively short time, on an outpatient basis. However, complications have been observed. Bleeding, requiring blood transfusion was seen in two out of 15 procedures for islet transplantation [17]. In a cohort of 15 patients receiving intra-portal islets by this technique, one case of haemothorax and one case of haemoperitoneum occurred [2]. In a group of 170 patients with portal hypertension, intra-peritoneal bleeding was seen in 10.6%, intra-peritoneal bile leakage in 1.8%, and arterio-venous fistula in 0.6% [12]. Another study in a heterogeneous patient population described a clinically relevant complication rate of 9.2%. This included intra-abdominal haemorrhages in 5.1% cases [8]. These complications are less probable with the laparoscopic method, however a general anaesthetic is required, and the operating time is longer.

Trans-jugular intra-hepatic porto-systemic shunts (TIPS) are used for treatment of end-stage portal hypertension. In adapted form, this technique could serve as an alternative method to reach the portal system, probably with a lower risk of bleeding. However, this procedure is technically more challenging and time consuming than the percutaneous technique. This approach has not yet been described for islet transplantation. The currently used techniques disperse the islets throughout the entire liver. In this study, we chose to use a well-defined liver segment to harbour the islets. This was made possible by the use of fluoroscopy and a smooth guide-wire during the laparoscopy. MRI studies demonstrated that the islets were engrafted in the liver segments where they were primarily injected. We believe that the ability to localise the grafts with more precision could offer several advantages.

We assumed that occurrence of any septic complication, for instance a liver abscess, would be considered a localised one, and percutaneous drainage would be a feasible solution. Abnormal proliferation and subsequent neoplastic growth of the transplanted cells or the hepatic tissue have not been observed in human islet transplantation, but is of theoretical concern [6, 7]. A curative local resection would be more feasible when the graft implantation site is limited to a defined part of the liver, should this occur. Therefore, we prefer the use of a defined liver segment for islet transplantation over diffuse liver infusion. Portal hypertension is another potential danger of intra-portal implantation, especially when islet cells are dispersed diffusely, and high volumes of cells are injected. In the present study, no rise in portal pressure was observed after injection of the cell suspension.

We encountered no immediate or late surgical complications in our patients. This method offers the possibility of a step-by-step control in guiding and fixing a non-traumatic catheter into a selected portal branch of the liver. Totally implantable venous access systems are suitable for long-term chemotherapy in cancer patients and cause few complications [11]. Currently, an additional graft is frequently required to reach or maintain insulin independency. The use of the latter device makes the subsequent injections of additional islets in the same patient possible, without the need for new surgery. Furthermore, this device allows the local administration of drugs (heparin, etc.) at the transplantation site. In our patient group, there were no infectious or other complications due to the venous access device. On the other hand, it is important that the implantation period be kept as short as possible to minimise the risks of septic or thrombotic complications. We conclude that the laparoscopic approach for islet transplantation is a relatively easy and safe technique, which could serve as an alternative technique for islet transplantation.

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