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Pediatr Surg Int (2013) 29:1065–1070
DOI 10.1007/s00383-013-3392-7

ORIGINAL ARTICLE

Impact of pediatric intestinal transplantation on intestinal failure in Japan: findings based on the Japanese intestinal transplant registry

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Published online: 28 August 2013

Abstract
Introduction We assessed the impact of intestinal transplantation on Japanese pediatric patients with intestinal failure with data from the Japanese intestinal transplant registry.
Methods Standardized forms were sent to all known intestinal transplantation programs, requesting information on transplants performed between 1996 and June 30, 2012. Patients younger than 18 years were analyzed. Patient and graft survival estimates were obtained using the Kaplan–Meier method.
Results Of the 14 intestinal transplants, 4 were deceased and 10 were living donor transplants. The primary indications were: short gut syndrome ($n = 7$), intestinal functional disorder ($n = 6$), and re-transplantation ($n = 1$). The overall 1- and 5-year patient survival rates were 77 and 57 %, respectively. In transplants performed after 2006 ($n = 6$), the one-year patient survival rate was 83 %, and the 5-year survival rate was 83 %. Graft one- and 5-year survival rates were 83 and 83 %, respectively. The living-related transplant survival rate was 80 % at 1 year and 68 % at 2 years, compared to 67 and 67 % for cadaveric transplant recipients. There were no statistically significant differences in patient ($p = 0.88$) and graft ($p = 0.76$) survival rates between living donor and cadaveric transplant recipients. All current survivors discontinued PN.
Conclusion Intestinal transplantation has become an effective therapy for patients with intestinal failure who cannot tolerate PN.

Keywords Intestinal transplant · Pediatric transplant · Japanese registry

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Introduction

Intestinal failure is caused by a critical reduction of functional gut mass to below the minimal amount necessary for adequate digestion and absorption to satisfy nutrient and fluid requirements for maintenance in adults and growth in children [1]. The most common type of intestinal failure is short bowel syndrome with an estimated incidence of 3–5 cases per 100 000 births per year

[2]. Advances in neonatal intensive care, anesthesia, nutritional support, and surgical techniques have improved the survival of children, so the prevalence of common causes of short bowel syndrome, including gastroschisis, necrotizing enterocolitis, and intestinal atresia has likely increased in recent years [3]. Some survivors, however, develop irreversible intestinal failure. The prognosis for intestinal failure related to short gut syndrome and intestinal motility disorders has improved dramatically owing to the development of parenteral nutrition (PN). Some children achieve long-term survival with PN at home with a relatively good quality of life, but others develop serious side effects that can eventually lead to death. However, PN-related complications, such as loss of venous access and intestinal failure-associated liver disease (IFALD), are still major problems for patients with intestinal failure [4]. Intestinal transplantation can significantly improve their prognosis and quality of life. Early efforts to transplant the small bowel have failed due to refractory graft rejection and sepsis. Outcomes improved during the early 1990s, but survival rates were still inferior to those for other organ transplants. Over the past 5 years, individual centers have reported improved outcomes with better long-term intestinal engraftment.

The first intestinal transplant in Japan was performed in 1996. The total number of intestinal transplants in Japan has increased to 24 as of June 2011. We assessed the impact of intestinal transplantation on Japanese pediatric patients with intestinal failure based on data from the Japanese intestinal transplant registry.

Methods

Standardized forms were sent to all known intestinal transplantation programs, requesting information on intestinal transplants performed between 1996 and June 30, 2012. The data included age, sex, date of birth, date of transplant, type of donor (deceased or living), pre-transplant status (home or hospital), underlying disease, procedure, ABO blood type, immunosuppression regimen (induction and maintenance therapy), and post-transplant status (PN requirement, intravenous (IV) fluid requirement, and daily life restrictions). Patients under 18 years of age were analyzed. The data were entered into a Microsoft Excel spreadsheet and analyzed with JMP version 10.0 (SAS Institute Inc, USA). Patient and graft survival estimates were obtained using the Kaplan–Meier method. For survival analysis, failure was defined as occurring on the date of graft removal or death. A p value <0.05 was considered statistically significant. This study was approved by the institutional review board.

Results

Four programs provided data on 14 grafts in 13 patients who were received transplants between 1 April 1996, and 30 June 2012 in Japan. The participation rate was 100 %. All intestinal transplants performed in Japan are captured in the registry database. All patients were followed, unless the patient has passed way. Ten grafts were obtained from living donors, and four cases involved deceased donors. The annual number of intestinal transplants, according to organ donation type, is shown in Fig. 1. Prior to 2005, 25 % of patients who underwent transplantation were called in from home, as compared with 66 % in the last 5 years (Fig. 2).

There were nine male and five female recipients. The age distribution of the recipients is shown in Fig. 3. Two-thirds of the patients were over 6 years old. The youngest recipient was 8 months. The causes of intestinal failure requiring intestinal transplantation are shown in Fig. 4. Approximately half of the patients had conditions that result in short gut syndrome.

Most patients ($n = 13$) received isolated intestinal transplants. There was only one case of simultaneous liver-intestinal transplantation from two living-related donors. Twelve patients received grafts from donors with an identical ABO blood type. Two patients received grafts from ABO compatible donors. There were no transplants involving ABO incompatibility. All patients were on tacrolimus maintenance therapy. The types of induction therapy used are shown in Fig. 5. Antibody-based induction therapy and tacrolimus-based maintenance immunosuppression were used even if the medication was not commercially available in Japan.

Graft and patient overall survival as of June 2011 are shown in Kaplan–Meier plots (Fig. 6a, b, respectively). The one-year and 5-year patient survival rates were 77 and 57 %, respectively, comparable with rates from the international intestinal transplant registry. Five recipients died.

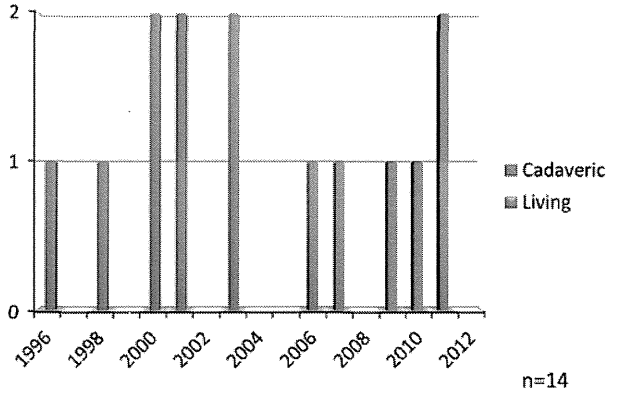

Fig. 1 Number of intestinal transplants by year

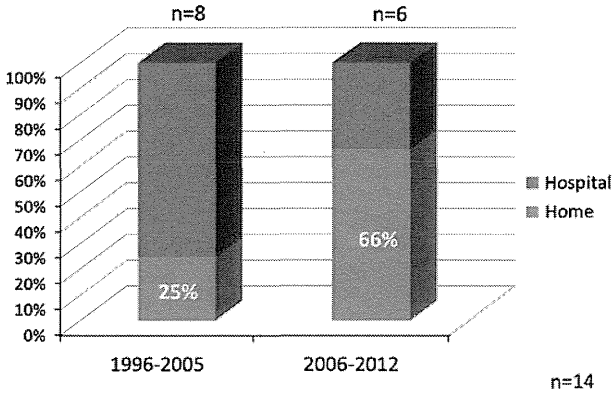

Fig. 2 Pre-transplant patient status

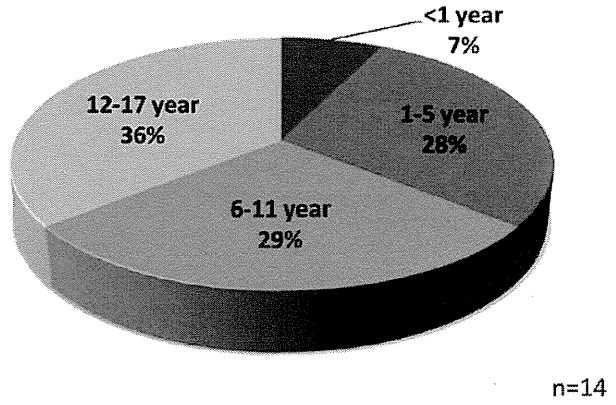

Fig. 3 Recipient age at transplant

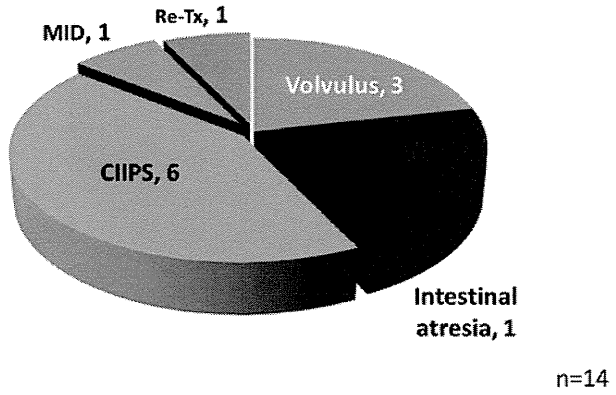

Fig. 4 Cause of intestinal failure *NEC* necrotizing enterocolitis, *CIIPS* chronic idiopathic intestinal pseudo-obstruction syndrome, *MID* microvillus inclusion disease, *Re-Tx* Re-transplant

The causes of death included sepsis ($n = 3$), post-transplant lymphoma ($n = 1$) and intra cranial hemorrhage ($n = 1$).

The 1-year overall graft survival rate was 80 % for cadaveric grafts versus 50 % for living donor grafts ($p = 0.76$), as shown in Fig. 7a. The 1-year overall patient survival rate was 80 % for cadaveric grafts versus 67 % for living donor grafts ($p = 0.88$), as shown in Fig. 7b.

Graft survival improved over the last 5 years. The one- and five-year graft survival rates were 83 and 83 % for 2006–2011 versus 63 and 38 % for 1996–2005 ($p = 0.14$), as shown in Fig. 8a. The 1- and 5-year patient survival rates were 83 and 83 % for 2006–2011 versus 71 and 43 % for 1996–2005 ($p = 0.27$), as shown in Fig. 8b.

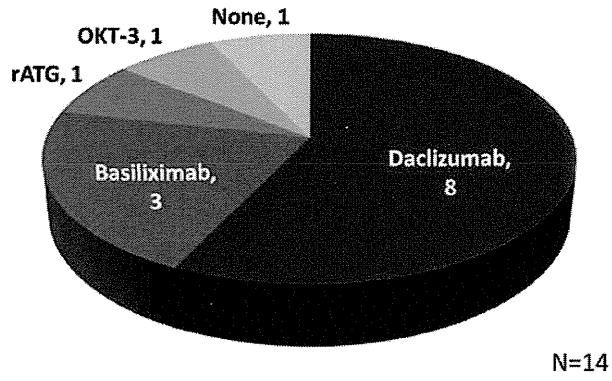

Fig. 5 Induction immunosuppression therapy *rATG* rabbit anti-thymus globulin, *OKT-3* anti-CD3 monoclonal antibody

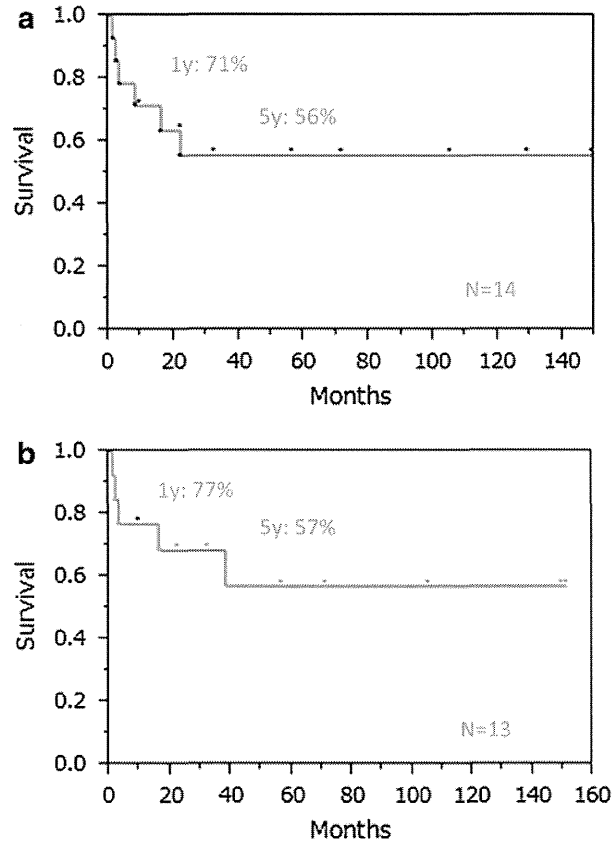

Fig. 6 Overall graft (**a**) and patient (**b**) survival

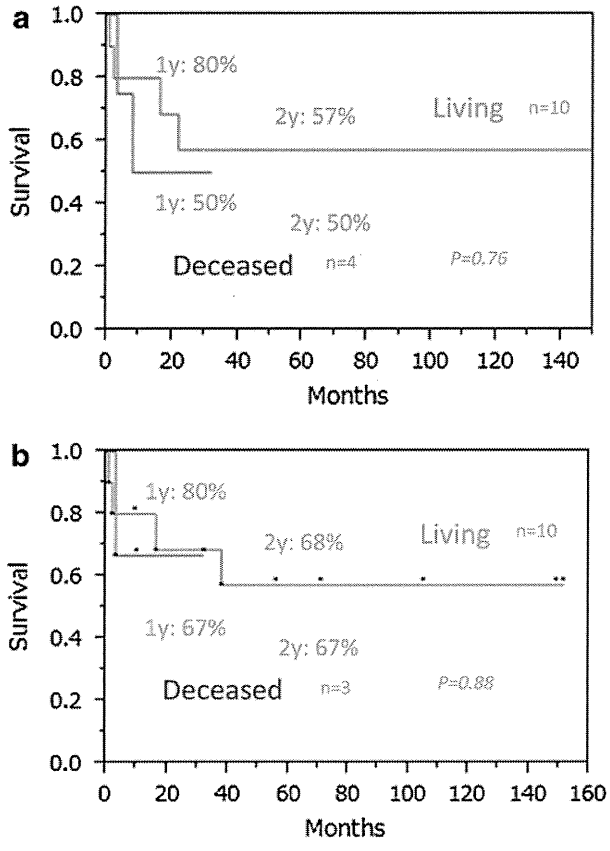

Fig. 7 Graft (**a**) and patient (**b**) survival according to graft type

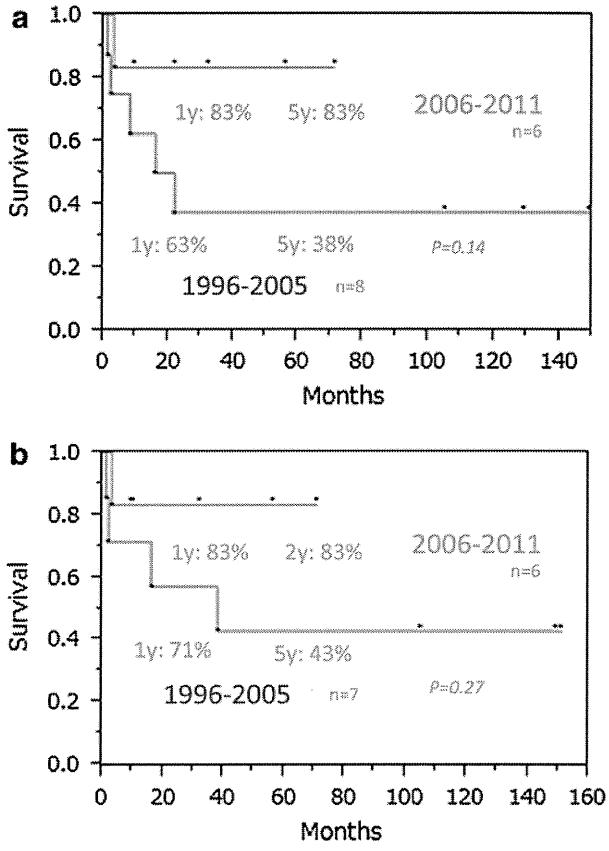

Fig. 8 Graft (**a**) and patient (**b**) survival by era

Graft function in terms of PN dependence was excellent. All patients became PN-free after intestinal transplantation, although two-thirds of patients require continuous or intermittent intravenous fluid support. Of the eight patients who were alive at the time of data collection, all patients were off parenteral nutrition, with three patients requiring intravenous fluids daily, two patients requiring intravenous fluids occasionally (Fig. 9). Most recipients stopped parenteral supplementation, eat, and have resumed normal activities. Of the seven surviving patients 1 year after transplant, six lead a full life.

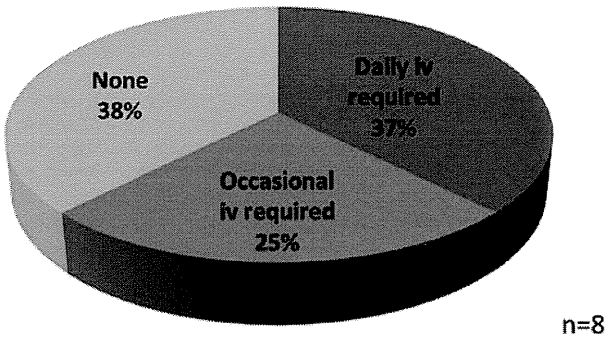

Fig. 9 Intravenous (IV) fluid requirement after intestinal transplantation

Discussion

Children with intestinal failure are at risk for numerous complications, especially PN-related complications. For example, loss of venous access and IFALD are still major problems for patients with intestinal failure because they are potentially life-threatening [4].

Catheter-related bloodstream infections were common in patients with intestinal failure [5]. Survival of children with chronic intestinal failure has increased as result of home PN. Adequate central venous accesses crucial for the successful management of home PN, but venous access can be complicated by episodes of catheter-associated infection, repeated procedures to replace catheters, and catheter-related thrombosis. Management and prevention of catheter-related thrombosis are of vital importance. [6].

IFALD can be a progressive and fatal entity in children with short gut syndrome. Parenteral fish oil-based fat emulsions are safe and may be effective in the treatment of PN-associated liver disease [7]. A lipid reduction protocol may prevent cholestasis [8]. Despite all efforts to prevent

complications, some children develop end-stage intestinal failure.

As outcomes of intestinal transplantation have improved, it has become the definitive treatment for patients with intestinal failure who cannot tolerate PN. Over the past decade, intestinal transplantation has become accepted as standard therapy for patients with life-threatening complications of PN in many countries [9, 10].

Currently, evaluation for transplant is recommended for pediatric patients with intestinal failure who are doing poorly on PN due to loss of more than 50 % of the major intravenous access sites (two out of four sites include both internal jugular veins and subclavian veins); recurrent severe catheter-related sepsis; progressive liver dysfunction; or impaired renal function due to massive gastrointestinal fluid loss.

Timely referral to an intestinal transplant program is important for children with intestinal failure because intestinal transplantation is easier and safer with adequate central venous access and normal liver function [11]. For patients who undergo intestinal transplantation, patient survival is similar to remaining on PN. The inclination is therefore to move towards earlier transplantation and avoiding the need for concomitant liver transplantation [12].

The 2011 report of the intestinal transplant registry confirmed that intestinal transplantation has become a definitive therapeutic option for patients with intestinal failure. By 2011, 2,611 intestinal transplants had been performed throughout the world with 79 participating centers worldwide. Three types of intestinal transplantation are performed: (1) isolated intestinal transplantation (1,184 cases); (2) liver and intestine transplantation (845 cases); and (3) multivisceral transplantation (619 cases). In pediatric patients, two-thirds acquired short gut syndrome as a result of congenital disease, including gastroschisis, intestinal atresia, and necrotizing enterocolitis [10].

On the other hand, only 14 intestinal transplants have been performed in patients under 18 years of age in Japan. The number is relatively small, although it is estimated that 40 pediatric patients require intestinal transplants nationwide [13]. In the Japanese experience, the 1- and 5-year overall patient survival rates are 77 and 57 %. The one-year survival rate was 83 % for the last 5 years. These are considered acceptable results for the treatment of intestinal failure. Our results in Japan are comparable with results worldwide, even though there are only one or two cases per year performed in Japan compared to over 100 intestinal transplants yearly performed in the world. In our opinion, children with intestinal failure should be treated with intestinal transplantation in Japan as well as in other countries when feasible.

There were two major reasons for the low number of intestinal transplants in Japan. One reason is the lack of available organs. For a long time, relatively few donations from deceased donors were obtainable in Japan. As with other solid organs, most intestinal transplants in Japan are performed with living-related donors. Although the situation has changed due to the new Act on Organ Transplantation, which went into effect in 2010, the number of deceased donations has not increased dramatically, especially among pediatric donors.

The financial barrier is the other, more profound reason preventing the greater use of intestinal transplantation in Japan. Since the procedure is not covered by health insurance, either the patient or the transplant center must pay the considerable costs out of pocket.

Some patients develop liver failure with short gut syndrome. These patients need simultaneous liver-intestinal transplants. A combined liver-intestine transplant has less risk of acute rejection than an isolated intestinal transplant because the liver may have protective effects on the intestine [10]. Combined liver and intestine transplants are the most frequent procedure in infants and children, accounting for half of the cases. Current organ allocation guidelines have not allowed for simultaneous combined liver–intestine organ retrieval until the law was revised in 2010; thus, simultaneous liver–intestine transplantation with a deceased donor graft had been impossible. Isolated intestinal transplantation, the preferred procedure, was offered to patients with limited IV access or recurrent line infections. Combined liver–intestine transplants are performed for treatment of irreversible liver disease caused by PN. Isolated intestinal transplantation from deceased donors following living-related liver transplantation, referred to as sequential combined liver-intestine transplantation, has been attempted.

Previously, the law on organ transplantation banned donors below 15 years of age. This is the main reason why there were relatively few pediatric transplant recipients. Intestinal transplant for infants was previously not possible because of donor-recipient size mismatch. Only a small number of pediatric transplants have been performed. Pediatric patients still await the opportunity to benefit from intestinal transplantation. Moreover, younger patients sometimes develop liver failure [3]. Multivisceral transplants are recommended for the treatment of severe gastrointestinal motility disorders [14]. However organ allocation guidelines do not allow for multivisceral organ retrieval. Further reform of allocation guidelines is needed.

This analysis found that improved induction immunosuppression is strongly associated with higher survival rates. The use of antibody induction therapy appears to be particularly important for the success of intestinal transplantation, possibly due to the large lymphoid mass of this type of graft [15]. Induction with rabbit anti-thymus globulin (rATG) minimized the amount of tacrolimus needed for

maintenance immunosuppression, facilitated the long-term control of rejection, and decreased the incidence of opportunistic infections, resulting in a high rate of patient and graft survival [16]. The combination of rATG and rituximab was an effective induction therapy according to our preliminary data. The number and severity of rejection episodes increased when the liver was not included as part of the graft. An immunosuppression regimen including rATG, rituximab, and steroids may have a protective effect against post-transplant lympho proliferative disease (PTLD) and chronic rejection [17]. Sirolimus is a safe rescue therapy in children with intestinal transplants when tacrolimus is not well tolerated. Renal function and hematologic disorders seem to improve, although other simultaneous strategies could be involved [18]. However, those medications are not commercially available with insurance coverage in Japan. Children after intestinal transplant should be managed with limited immunosuppression.

Preemptive assessments are recommended, even for patients doing well on PN, and for infants and adults with an ultra-short gut or for infants with total intestinal aganglionosis or microvillus inclusion disease, since patients with these findings have very poor survival rates on PN [15].

Early referral and listing are important for successful outcomes. Presently, because of the risks involved as well as financial reasons, transplants are rarely offered to pediatric patients in Japan. However, this treatment will undoubtedly become more common over time as the results of intestinal transplantation continue to improve.

Conclusion

Intestinal transplantation has become the definitive treatment for patients with chronic intestinal failure. Since intestinal transplantation in Japan has yielded satisfactory results, indications for the procedure should be expanded. The national health insurance should cover intestinal transplants to reduce the incidence of PN-related complications. Systems facilitating combined simultaneous liver–intestine and multi-organ transplants should be developed. We continue to work on reforming national health insurance coverage and realizing multi-organ transplantation in Japan.

Acknowledgments This research was partially supported by Health Labor Sciences Research Grant of Ministry of Health, Labor and Welfare, Japan. Japanese intestinal transplant registry is managed by the Japanese Society for Intestinal Transplantation. Also, the authors thank the following institutions for the cooperation in the survey.HBP Surgery and transplantation, Kyoto University: Pediatric Surgery, Tohoku University School of Medicine; Surgery, Keio University Graduate School of Medicine; Pediatric Surgery, Kyusyu University School of Medicine; Pediatric Surgery, Osaka University Graduate School of Medicine.

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Ann Surg Oncol (2014) 21:1391–1397
DOI 10.1245/s10434-013-3405-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Computed Tomography (CT) Venography Using a Multidetector CT Prior to the Percutaneous External Jugular Vein Approach for an Implantable Venous-Access Port

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ABSTRACT

Background and Purpose. The objective of this study was to determine the success rate and complications of using the percutaneous approach of the external jugular vein (EJV) for placement of a totally implantable venous-access port (TIVAP) with a preoperative estimate of the detailed anatomical orientation of the cervical venous plexus using computed tomography venography (CT-V).

Methods. A prospective cohort study of 45 patients in whom placement of a TIVAP was attempted via the right EJV was conducted. The preoperative anatomical estimation of the cervical venous plexus was performed with CT-V using a Multidetector Helical 16-section CT. The angulation between the right EJV and the right subclavian vein, anterior jugular vein, transverse cervical vein, and suprascapular vein was estimated.

Results. CT-V success was achieved in 45 of 45 patients (100 %). A plexus of veins under the clavicle was most commonly responsible for the insertion of the central venous catheter. The EJV approach resulted in a successful cannulation rate of 93 %. No initial complications of pneumothorax or carotid artery puncture occurred during insertion procedures. Late complications occurred in three patients. These included one port erosion (2 %), one catheter occlusion (2 %), and one wound hematoma (2 %). Catheter-related infections were observed in one patient (2 %).

Conclusions. The percutaneous EJV approach with CT-V guidance is an optional method for patients with multiple central venous cannulations, those in hemodialysis, or those with long catheter indwelling periods.

Central venous catheters (CVCs) and totally implantable venous-access ports (TIVAPs) are used for total parenteral nutrition (TPN), medication administration, chemotherapy, and hemodynamic monitoring.[1] The preferred access approach for CVC placement is the right subclavian vein (SCV) or the right internal jugular vein (IJV). This technique carries a risk of complications, including pneumothorax, hemothorax, and arterial puncture, which can cause significant morbidity.[2–6] Although the left IJV and right SCV have been used for secondary access, several studies suggest that both the SCV and the IJV should be avoided because of a high incidence of procedural complications, as well as central stenosis and thrombosis. The occurrence of these complications is increased in patients undergoing hemodialysis and in those with a history of multiple central venous catheterizations.[5–8] Before using the SCV, access via the external jugular veins (EJVs) should be attempted.[4,9,10] The EJV cut-down approach has to be considered a valid, safe, and suitable alternative when the cephalic vein is not feasible.[11,12] EJV catheterization as a CVC placement route is commonly believed to be difficult because of its anatomical problems.[13] Variations at the

First Received: 12 August 2013;
Published Online: 4 December 2013

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terminal point and angulation of the EJV as it enters the SCV contribute to a high failure rate.[14] Venography performed from multiple access sites may be required to identify a suitable vein for central access. The EJV approach without venography resulted in a successful cannulation rate of 81 % in our previous study. In this study, we describe our clinical experience with percutaneous venous access via the EJV for TIVAP placement with preoperative anatomical estimation through computed tomography (CT) venography (CT-V) using a multidetector helical 16-section CT (MDCT).

PATIENTS AND METHODS

This study was approved by our hospital's Institutional Review Board. All patients referred to us for TIVAP placement through the right IJV underwent clinical and ultrasound examinations of the right side of the neck. If there were obstacles to the placement of a TIVAP through the right IJV, such as IJV occlusion or skin infection overlying the right IJV, a preoperative CT-V was planned before the TIVAP placement. This was a prospective cohort study of consecutively treated adults (range 74–94 years of age) who underwent attempts at TIVAP placement via EJV while receiving care in our hospital. We conducted a prospective observational study of 45 patients over a 20-month period from September 2011 through March 2013. Women accounted for 56 % ($n = 25$) of the study population, with a mean age of 76 years (range 55–94 years). Mean age of the male participants was 79 years (range 75–89 years). The 32 patients had a history of CVC insertion through the right IJV, both IJVs, or SCVs, ranging from one to three catheterizations with mean of 1.6 catheterizations. Two patients had a history of non-tunneled catheters for temporary hemodialysis. The indication for TIVAP placement was TPN in 31 patients (69 %), chemotherapy for solid and hematologic malignancies in four patients (8 %), and long-term antibiotic administration or blood transfusion in three patients (6 %). Patients with impaired renal function were excluded from this study. The choice of insertion route was based on the angulation between the EJV and the cervical venous plexus on CT-V. The catheter course and tip location were verified by a radiograph on the 1st, 7th, and 30th day, as well as at 6 and 12 months after insertion. The data included the inability to thread the catheter centrally, eventual CVC location, CVC adjustments needed, initial complications (pneumothorax and carotid artery puncture), late complications including catheter occlusion, catheter transection, catheter migration, symptomatic venous thrombosis, wound hematoma, port erosion, operating time, dwell time (time from insertion to removal), and catheter-related infection rate. A major procedural complication was one requiring active intervention, and a minor procedural complication required only conservative therapy. Premature TIVAP removal was defined as removal for causes other than patient demise, termination of therapy, or termination of study. Symptomatic venous thrombosis was clinically assessed according to whether symptoms such as facial edema and right-arm swelling with or without pain developed after the EJV catheterization, including the follow-up MDCT and ultrasonography studies. Catheter-related infection included insertion site infection and catheter-related bacteremia. Insertion site infection was defined as infection localized to the catheter exit. Line sepsis is equivalent to catheter-related bacteremia,[4] which was defined as a clinical episode of sepsis in which there was a high index of clinical suspicion that the catheter was the source of the sepsis.

Scanning Parameters

The CT-V was performed with a 16-MDCT scanner (BrightSpeed Elite SD, GE Healthcare, Fairfield, CT, USA). The CT-V of the cervical area involved scanning from the base of the C1 vertebral body to the level of pulmonary hila after a fixed 40-s delay between the onset of the contrast material injection and the start of scanning. A 100 mL volume of non-ionic iodinated contrast material (Iopamiron 300™, Bayer HealthCare, Leverkusen, Germany) was injected into a right antecubital vein at a rate of 3 mL per second using a power injector. The following scanning and reconstruction parameters were used for the multidetector CT venogram acquisition: 1.25-mm collimation; pitch of 1.375; a 1.25-mm reconstruction increment; and a 0.8-s rotation time. A low-dose technique was used, with a tube current of 100–250 mAs and a peak kilovoltage of 120 kVp. The technique values for the multidetector row CT used in this study (120 kVp, 50 mA) were chosen so that the image noise would match that found with the single-section technique (120 kVp, 70 mA). The pitch needed to be varied to account for differences in patient length so that the acquisition could be completed in 30 s. After scout images were acquired, images with the patient in the supine position were obtained. The MDCT scans were acquired from the level of the C1 vertebral body to the level of pulmonary hila with z-axis coverage of 32–38 cm and with the patient in a supine position. Standard maximum intensity projection images of the major cervical venous structures were created by the three-dimensional (3D) laboratory. A primary two-dimensional (2D) evaluation technique (axial views, 2D-CT) was applied using multiplanar reformatted (MPR) images and a 3D view. GE Navigator software enabled the simultaneous review of 3D-CT vessels, coronal and sagittal MPR, and axial images.

Image Analysis

Image processing was performed with a workstation (2LCD Workflow, GE, Healthcare for Linux) using a combination of soft-tissue windows (window width 400 HU; window level 40 HU) and bone windows (window width 2,000 HU; window level 0 HU), multiplanar reformats, and 3D problem solving. Data were examined using transverse CT images with the concurrent display of both 2D and 3D reformatted images for measuring the angulation between vessels with a 3D workstation (BrightSpeed Elite SD). The reconstructed images were analyzed for parameters with implications for the CVC placement, including the angle of the EJV at four locations: the angle between the left EJV and the SCV, the angle between the left EJV and the anterior jugular vein (AJV), the angle between the left EJV and the transverse cervical vein (TCV), and the angle between the left EJV and the suprascapular vein (SSV). We examined the data to assess which junction was most responsible for the insertion of a CVC.

Percutaneous Insertion Technique for EJV

The patient was placed in a 20° Trendelenburg position to distend the EJV, and patency was confirmed by ultrasonography. An anesthetic patch was attached to the insertion site of the skin before catheter insertion. The right side of the neck and the upper chest of the patient were prepared with sterile technique. The right EJV was identified by visual inspection and palpation, and then punctured. An EJV puncture was performed under sterile conditions with a 14-gauge introducer needle (over-the-needle Teflon catheter, BD Insyte I.V. Catheter^{TM}, Becton–Dickinson, Infusion Therapy Systems, Inc., Sandy, UT, USA) (Fig. 1a, b). The Seldinger technique was used to access the EJV with dilators and peel-away sheaths for the insertion, which used an 18-gauge polyurethane CVC (Bard Access Port, SlimPort 6F^{TM}, Bard Access system Inc., Salt Lake City, UT, USA) that was 75 cm in length (Fig. 1c). Under fluoroscopic control, the catheter was driven toward the SCV, the innominate vein, and finally the SVC, where the tip of the catheter was positioned. A port was placed in a tight subcutaneous chamber, over the pectoralis fascia, 4 cm under the clavicle (Fig. 1d). In cases where the preoperative CT-V demonstrated a sharp angulation of the EJV to the SCV (EJV–SCV sharp-angle type), an obtuse angulation between the EJV and the AJV (EJV–AJV obtuse-angle type), or an obtuse angulation between the EJV and the TCV or the SSV (EJV–TCV/SSV obtuse-angle type), which might cause difficulties in inserting the catheter or cause the catheter to become kinked or knotted, a guide wire (a 35-cm long, 0.089-cm diameter, flexible angiographic catheter guide wire: angle type, Radifocus guide wire M^{TM}, Terumo, Tokyo, Japan) technique[12] was used under fluoroscopy. In cases where the preoperative CT-V demonstrated an obtuse-angle type EJV–TCV/SSV, which might cause difficulties in inserting the catheter or cause the catheter to thread to the SCV, an ultrasound-guided right femoral vein (FV) cannulation was used.[13,14] Chest radiographs (CXRs) were obtained after the procedure.

RESULTS

A total of 45 patients were enrolled in the study. Successful CT-V was achieved in 45 of 45 patients (100 %) (Fig. 2a, b). There were no complications from the CT-V in any of the 45 patients. Mean angulation between the right EJV and the right SCV was 144° ± 36° in the obtuse-angle cases (88 %) (Fig. 3a) and 72° ± 28° in the EJV–SCV sharp-angle type (12 %) (Fig. 3b). Mean angulation between the EJV and the AJV was 125° ± 12° in the EJV–AJV obtuse-angle type (10 %) and 45° ± 5° in the sharp-angle cases. Mean angulation between the EJV and the TCV or SSV (Fig. 3c) was 133° ± 5° in the EJV–TCV/SSV obtuse-angle type (8 %) and 61° ± 20° in the sharp-angle cases (Fig. 3d). Central venous access via the EJV was obtained in 42 (93 %) of 45 patients. The average number of puncture attempts was 1.45 (range 1–4) and the average procedure time was 13.5 min (range 9–25 min). In ten patients, the preoperative CT-V demonstrated a sharp-angle type EJV–SCV, an obtuse-angle type EJV–AJV, or an obtuse-angle type EJV–TCV/SSV [15] (Table 1). In seven of the patients with an EJV–SCV sharp-angle type (four patients) or an EJV–AJV obtuse-angle type (three patients), TIVAP placement via EJV was obtained using a Radifocus guide wire M^{TM} technique under fluoroscopy after the J-guide wire technique failed. In the three patients with an obtuse-angle type EJV–TCV/SSV, right FV cannulation was used. In the remaining 35 patients, the catheters were inserted via the right EJV without any problem. Successful placement of a TIVAP was accomplished in all patients. The catheter dwell time ranged from 65 to 325.5 days, with a mean dwell time of 255.5 days. There were no significant procedural complications (pneumothorax, expanding hematoma, or carotid artery puncture) during the 43 catheterization attempts. In five patients (12 %), a small amount of subcutaneous bleeding over the EJV was observed. Late complications occurred in three patients. These included one port erosion (2 %), one catheter occlusion (2 %), and one wound hematoma (2 %). Catheter-related infections were observed in one patient (2 %). The catheter-related infection was catheter-related bacteremia, which occurred at 65 catheter days in a patient undergoing chemotherapy who had the catheter removed (Fig. 4). No thrombotic complications were demonstrated.

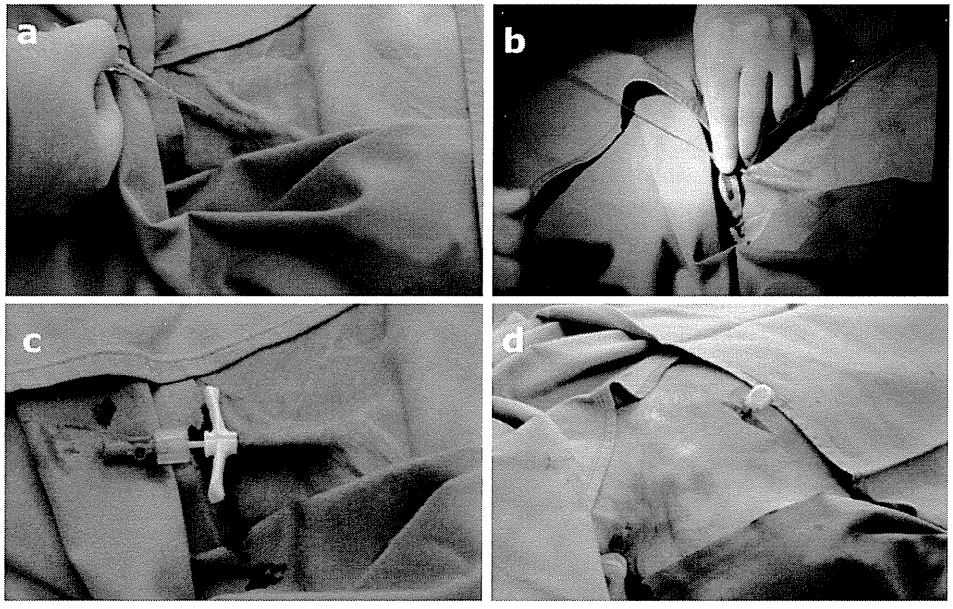

FIG. 1 **a** Puncture of a right EJV was attempted with a 16-gauge over-the-needle Teflon catheter. **b** The J-guide wire was inserted and advanced into the central venous position. **c** The dilator and peel-away sheath were inserted over the wire and then an 18-gauge, 20 cm polyurethane radiopaque catheter was inserted in a smooth, one-step maneuver. **d** A port was placed in a tight subcutaneous chamber, over the pectoralis fascia, 4 cm under the clavicle

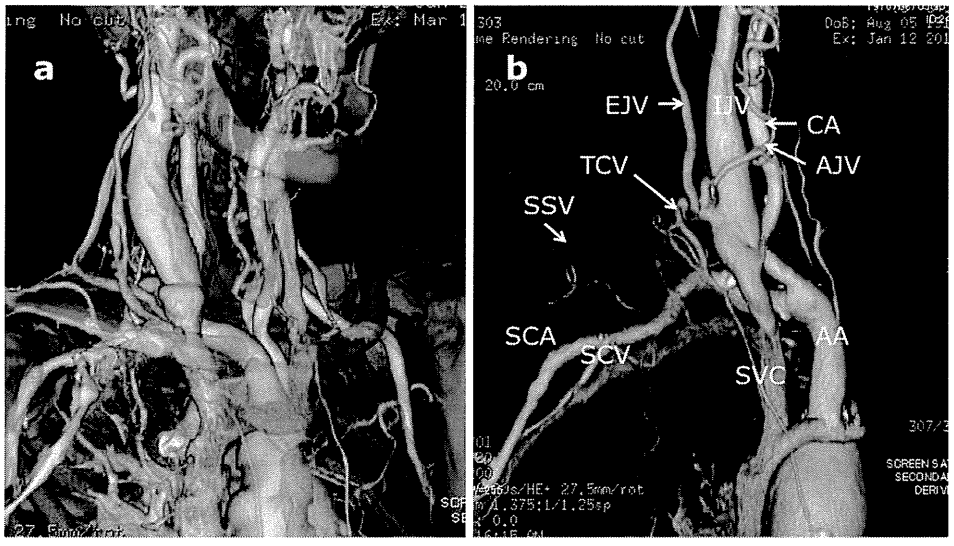

FIG. 2 MDCT venography of the cervical venous plexus: antero-posterior volume-rendered images (**a**, **b**). The CT-V showed a detailed cervical venous plexus and the central venous system. It also clearly revealed individual vascular anatomies around the EJV and SCV junction. *MDCT* multidetector computed tomography, *CT-V* computed tomography venography, *EJV* external jugular vein, *SCV* subclavian vein, *IJV* internal jugular vein, *CA* carotid artery, *AJV* anterior jugular vein, *TCV* transverse cervical vein, *SSV* suprascapular vein, *SCA* subclavian artery, *SVC* superior vena cava, *AA* aortic arch

DISCUSSION

The technique of central venous catheterization via the EJV was reported in 1974.[9] The EJV approach has not been popular because of its low success rate,[13] which is due to further anatomical considerations. Although the EJV cut-down approach for central venous access is well described in the literature,[11] there are few data available that specifically address the potential utilization of EJV for TIVAP placement. In this study, the success rate of the EJV puncture approach was 93 %, whereas the success of the CV cut-down approach has been reported as 93 %.[12] The

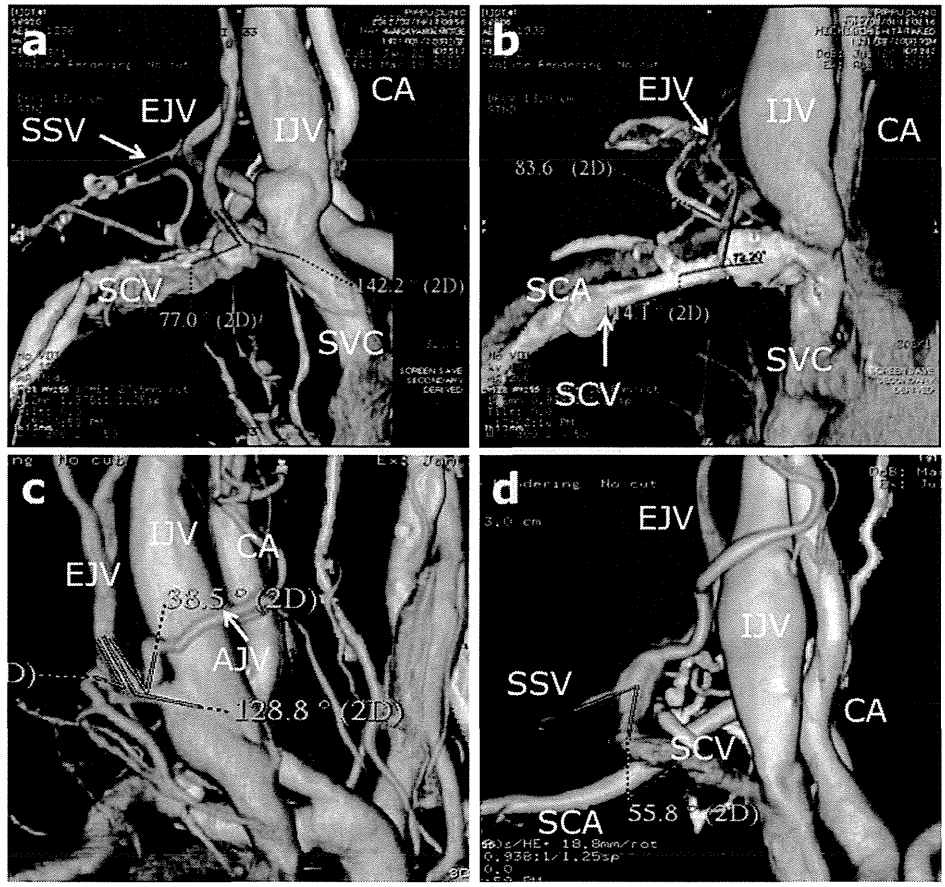

FIG. 3 MDCT venography: (**a**, **b**) anteroposterior volume-rendered images. The CT-V showed the angle between the right EJV and the right SCV. Mean angulation between the EJV and the SCV measured 144° ± 36° in the obtuse-angle cases (**a**), and 72° ± 28° in the sharp-angle cases (**b**). Mean angulation between the EJV and the AJV measured 133° ± 5° in the obtuse-angle cases (**c**). Mean angulation between the EJV and the SSV measured 61° ± 20° in the sharp-angle cases (**d**). *MDCT* multidetector computed tomography, *CT-V* computed tomography venography, *EJV* external jugular vein, *SCV* subclavian vein, *AJV* anterior jugular vein, *SSV* suprascapular vein

TABLE 1 Angulation between the right EJV and SCV or AJV or TCV/SSV

Angulation type	SCV	AJV	TCV/SSV
Sharp	70 ± 29 (14)	45 ± 13 (95)	62 ± 26 (92)
Obtuse	140 ± 30 (86)	132 ± 15 (5)	137 ± 8 (8)

Data are presented as mean angulation (degree) (%)

EJV external jugular vein, *SCV* subclavian vein, *AJV* anterior jugular vein, *TCV* transverse cervical vein, *SSV* suprascapular vein

benefits inherent in the use of the EJV include its large size and a greater ability to accommodate large or multilumen catheters more easily than many peripheral insertion sites, the superficial location, the ability to visualize the EJV without imaging technology, and the ease of access in reaching the SVC. The angulation between the EJV and the TCV/SSV was responsible for insertion success in our preliminary study. Catheterization from the EJV requires a detailed anatomical orientation of these vessels, including the central vascular system, before catheter insertion. Three-dimensional CT-V using MDCT clearly revealed individual vascular anomalies around the EJV and the SCV junction and could play an important role in safe cannulation. When compared with the IJV or SCV sites, the EJV site offers a small risk of bleeding, puncture of the carotid artery, or pneumothorax in frail, elderly patients.

The development of contrast-induced nephropathy (CIN) is related to the number of risk factors present, with the most important being renal insufficiency, diabetes mellitus, and volume of contrast agent used. Most studies show that, within a class, higher volumes (>100 mL) of iodinated contrast medium are associated with a higher risk for CIN.[16] There is evidence that low-osmolar contrast media are less nephrotoxic than high-osmolar contrast media in patients at increased risk for CIN.[16] We recommended that the dose not exceed 100 mL of non-ionic iodinated low-osmolar contrast agents in the CT-V.[17]

Our results demonstrate that percutaneous EJV cannulation is safe for central venous access, with a high success rate compared with other sites. Superficial hematoma was the only problem found with the EJV route in our study, and it was most often observed in the failed attempts. The site for percutaneously inserted catheters is determined by multiple factors, including the clinical status of the patient, the purpose of central access, the anticipated length of time it will be needed, and physician experience.[11] The most important advantage is the absence of major complications.

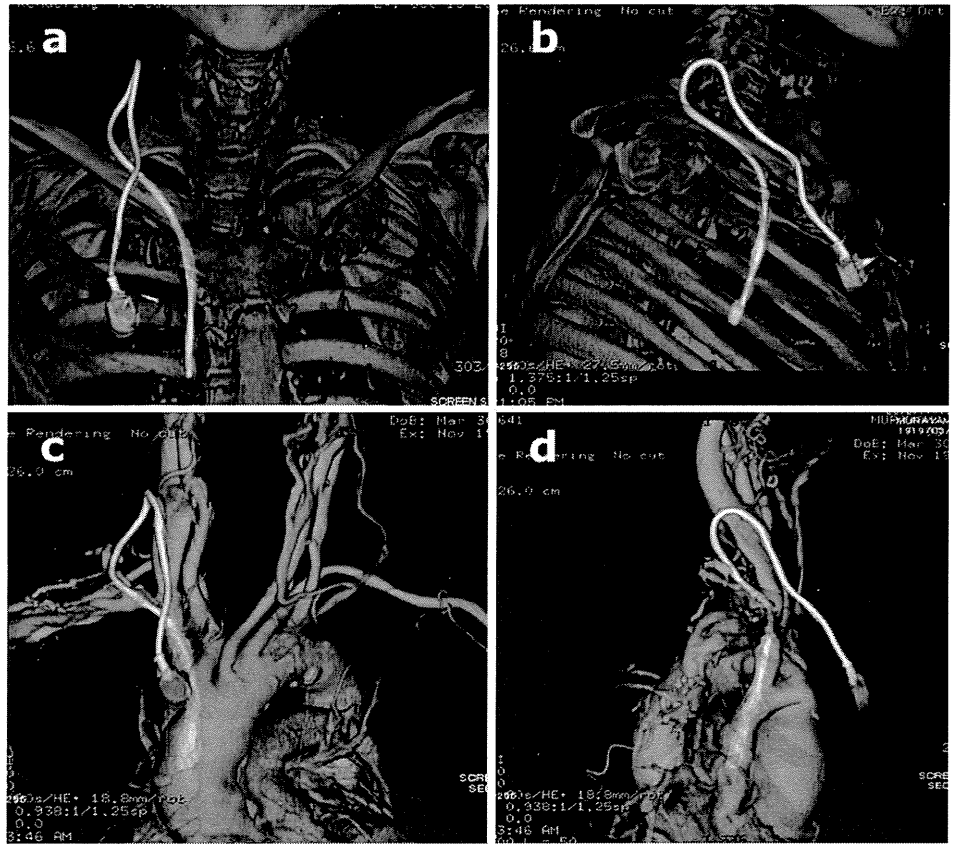

FIG. 4 Follow-up MDCT: anteroposterior (**a**) and lateral (**b**) volume-rendered images. Follow-up MDCT venography: anteroposterior (**c**) and lateral (**d**) volume-rendered images. The MDCT showed the appropriate TIVAP position and the catheter position. *MDCT* multidetector computed tomography, *TIVAP* totally implantable venous-access port

In regard to patient safety, it is worth nothing that in the relatively recent past, the use of peripherally inserted central catheters has obviated some of the risks involved with more central access sites. Therefore, central venous access via the EJV for the placement of TIVAP seems to be an option to consider for vascular access in patients, given our findings of a high success rate and a low complication rate.[18]

The present study has some limitations. Our study was preliminary in its prospective nature and the lack of a control group. The number of reported cases is relatively small, which implies the need for a study involving a large patient population that would permit a more precise assessment. Further studies are needed to determine how these advances in central access compare with the safety profile of the EJV technique with CT-V for the placement of a TIVAP.

CONFLICT OF INTEREST None of authors have identified any conflicts of interest.

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Journal of Investigative Surgery, 27, 176–182, 2014

ISSN: 0894-1939 print / 1521-0553 online
DOI: 10.3109/08941939.2013.865818

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NEW METHODOLOGIES

Central Venous Access via External Jugular Vein with CT-Venography Using a Multidetector Helical 16-Section CT

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ABSTRACT

Objective: To determine the success rate and complications of using the external jugular vein (EJV) for central venous access with a preoperative estimate of the detailed anatomical orientation of the cervical venous plexus using computed tomography venography (CT-V). *Design:* Prospective, observational human study. *Setting:* Surgical intensive care unit. *Patients:* Fifty-two patients who were undergoing EJV cannulations with CT-V using a Multidetector Helical 16-section CT (MDCT). *Intervention:* The preoperative anatomical estimation of the cervical venous plexus was performed with CT-V using an MDCT. In particular, the angulation between the EJV and the right subclavian vein (SCV) was measured. The anatomical abnormalities and the angulation between the EJV and the anterior jugular vein (AJV), transverse cervical vein (TCV), and suprascapular vein (SSV) were estimated. *Measurements and Main Results:* The success of CT-V was achieved in 52 of 52 patients (100%). The mean angulation between the right EJV and the right SCV was 144 ± 36 degrees in the obtuse-angle cases (88%) and 72 ± 28 degrees in the sharp-angle cases (12%). A plexus of veins under the clavicle was most commonly responsible for insertion of the central venous catheter (CVC). The EJV approach resulted in a 93% rate of successful cannulations. No complications of pneumothorax or carotid artery puncture occurred during insertion procedures. *Conclusions*: The EJV route is associated with comparable technical success and lower major procedural complication. The EJV approach with CT-V guidance is an option as the initial method when central venous cannulation must be performed under suboptimal conditions.

Keywords: external jugular vein (EJV); catheterization; central venous access; cervical venous plexus; multidetector helical 16-section computed tomography (MDCT); computed tomography venography (CT-V)

INTRODUCTION

Central venous access plays an important role in modern medical care. Central venous catheters (CVCs) are used for total parental nutrition, medication administration, chemotherapy, and hemodynamic monitoring [1]. The preferred access approach for CVC placement is the right subclavian vein (SCV) or the right internal jugular vein (IJV) [2, 3]. The percutaneous Seldinger method for catheter insertion into the SCV has been widely accepted, because of the ease of insertion when initially successful. This technique carries the risk of complications, including pneumothorax, hemothorax, and arterial puncture, that can cause significant morbidity [2, 4–6]. The right IJV approach should be considered as the primary access site for all patients [2, 7]. When the right IJV is not available for CVC placement, the second access site remains

Received 10 September 2013; accepted 11 November 2013.

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variable. Although the left IJV and both SCVs have been used for secondary access, several studies suggest that both the SCV and the IJV should be avoided because of a high incidence of procedural complications as well as central stenosis and thrombosis [4–6, 8]. These complications are increased in patients undergoing hemodialysis and in those with a history of multiple central venous catheterizations [4, 8].

The external jugular vein (EJV) approach for CVC placement has been reported [9, 10]. One reason to use the right EJV is its relatively straightforward course and short length, similar to the right IJV. A second reason is that the EJV is easily accessible, given its superficial location on the neck [11]. EJV catheterization as a CVC placement route is commonly believed to be difficult because of its anatomical problems. Variations at the terminal point and angulation of the EJV as it enters into SCV contribute to a high failure rate [12]. Of anatomic importance to catheterization is the fact that the EJV forms an acute angle at its insertion into the SCV, which may explain the higher rate of malpositioned catheters [13]. Venography performed from multiple access sites may be required to identify a suitable vein for central access.

Here, we describe our clinical experience with percutaneous venous access via the EJV with preoperative anatomical estimation through computed tomography venography (CT-V) using a multidetector helical 16-section CT (MDCT). We describe procedural techniques that improve the success rate in patients with more difficult venous access.

MATERIALS AND METHODS

This study was approved by our hospital's institutional review board, and a waiver of consent was granted because EJV central venous access was judged one of several routine access technique. This was a prospective cohort study of consecutively treated adults (76–91 years of range) who underwent EJV central venous access attempts while receiving care in our hospital. We conducted a prospective observational study over an 18-month period from September 2011 through March 2013 of 52 patients. Women accounted for 53% ($n = 27$) of the study population, with a mean age of 82 years (range, 76–91 years). The mean age of the male participants was 78 years (range 74–88 years). The indication for CVC placement: 41 patients (78%) were for parenteral nutrition (TPN), 6 patients (12%) were for chemotherapy for solid and hematologic malignancies, and 5 patients (10%) were for long-term antibiotic administration. Fifty-two patients underwent CT-V guided CVC placement, for which informed consent was obtained. The catheter course and tip location were routinely verified by a radiograph on the 1st and 7th day after insertion. The data included inability to thread the catheter centrally, eventual CVC location, CVC adjustments needed, initial and late complications, operating time, dwell time, and catheter-related infection rate. These data, including follow up data catheter removal, were complete for all patients within our institution. These data were recorded on a uniform data sheet by a stuff surgeon.

Scanning Parameters

The CT-V was performed with a 16-MDCT scanner (BrightSpeed Elite SD, GE Healthcare). The CT-V of the cervical area involved scanning from the base of the C1 vertebral body to the level of pulmonary hila after a fixed 40-s delay between the onset of the contrast material injection and the start of scanning. A 100-mL volume of nonionic iodinated contrast material (Iopamiron 300^{TM}, Bayer HealthCare, Leverkusen, Germany) was injected into a right antecubital vein at a rate of 3 mL/s using a power injector. The following scanning and reconstruction parameters were used for the multidectector CT venogram acquisitions: a 1.25-mm collimation, pitch of 1.375, a 1.25-mm reconstruction increment, and a 0.8-s rotation time. A low-dose technique was used, with a tube current of 100–250 mAs and a peak kilovoltage of 120 kVp. The technique values for the multi-detector row CT used in this study (120 kVp, 50 mA) were chosen so that the image noise would match that found with the single-section technique (120 kVp, 70 mA). The pitch needed to be varied to account for differences in patient length so that the acquisition could be completed in 30 s. All of the CT-V examinations were performed under the direct supervision of a radiologist with the ability to immediately interpret the images to ensure optimum image quality. After scout images were acquired, images with the patient in the supine position were obtained. The MDCT scans were acquired from the level of the C1 vertebral body to the level of pulmonary hila with a z-axis coverage of 32–38 cm and with the patient in a supine position. Standard maximum intensity projection images of the major cervical venous structures were created by the three-dimensional (3D) laboratory. A primary two-dimensional (2D) evaluation technique (axial views, 2D-CT) was applied using multiplanar reformatted (MPR) images and a 3D view. The GE Navigator software enabled the simultaneous review of 3D-CT vessels, coronal and sagittal MPR, and axial images.

Image Analysis

Image processing was performed with a workstation (2LCD Workflow, GE, Healthcare for Linux) using a combination of soft-tissue windows (window width, 400HU; window level, 40 HU) and bone windows (window width, 2,000 HU; window level, 0 HU), multiplanar reformations, and 3D problem solving. The

data were examined using transverse CT images with the concurrent display of both 2D and 3D reformed images for measuring the angulation between vessels with a 3D-workstation (BrightSpeed Elite SD). The reconstructed images were analyzed for parameters with implications for the CVC placement including the angle of the EJV at four locations: the angle between the left EJV and the SCV, the angle between the left EJV and the anterior jugular vein (AJV), the angle between the left EJV and the transverse cervical vein (TCV), and the angle between the left EJV and the suprascapular vein (SSV). We examined the data to assess which junction was most responsible for the insertion of CVC. The procedures were performed by a staff interventional radiologist.

Insertion Technique for External Jugular Vein

The patient was placed in a 20-degree Trendelenburg position to distend the EJV, and puncture site and patency were confirmed by ultrasonography. The right side of the neck and the upper chest of the patient were prepared with sterile technique. An anesthetic patch was attached to the insertion site of the skin before catheter insertion. The right EJV was identified by visual inspection and palpation and then punctured. An EJV puncture was performed under sterile conditions with a 14-gauge introducing needle (over-the-needle Teflon catheter, BD Insyte I.V. Catheter™, Becton Dickinson, infusion Therapy Sysems Inc., Sandy, Utah, USA). The Seldinger technique was used to access the EJV with a 16-gauge polyurethane central venous catheter (Argyle Medicut Catheter™, Tyco Healthcare, Tokyo, Japan), which is 30-cm in length. In cases where the preoperative CT-V demonstrated a sharp angulation of the EJV to the SCV (EJV-SCV sharp-angle type), or a obtuse angulation between the EJV and the AJV (EJV-AJV obtuse-angle type) or a obtuse angulation between the EJV and the TCV or the SSV (EJV-TCV/SSV obtuse-angle type), which might cause difficulties in withdrawing the catheter or cause the catheter to become kinked or knotted, a guide wire (a 35 cm long, 0.089-cm diameter, flexible angiographic catheter guide wire: angle type, Radifocus guide wire M™, TERUMO, Tokyo, Japan) technique [14] was used under fluoroscopy. In cases where the preoperative CT-V demonstrated the EJV-TCV/SSV obtuse-angle type, an ultrasound-guided right femoral vein (FV) cannulation [15] was used. Chest radiographs (CXRs) were obtained after the procedure. Manipulation of the CVC was made as necessary for acceptable placement. The procedures were performed by a staff surgeon.

RESULTS

A total 52 patients were enrolled over the study. The success of CT-V was achieved in 52 of 52 patients (100%) (Figures 1a and b). There were no complications from the CT-V in any of the 52 patients. The mean angulation between the right EJV and the right SCV measured 144 ± 36 degrees in the obtuse-angle cases (88%) (Figure 1c) and 72 ± 28 degrees in the EJV–SCV sharp-angle type (12%) (Figure 1d). The mean angulation between the EJV and the AJV measured 121 ± 10 degrees in the EJV–AJV obtuse-angle type (6%) (Figure 2a) and 43 ± 8 degrees in the sharp-angle cases (94%) (Figure 2b). The mean angulation between the EJV and the TCV or SSV measured 135 ± 4 degrees in the EJV–TCV/SSV obtuse-angle type (6%) (Figure 2c) and 63 ± 22 degrees in the sharp-angle cases (94%) (Figure 2d) (Table 1). Central venous access via the EJV was obtained in 50 (93%) of 52 patients. Fully completed data sheet were obtained from 50 patients. The average of number of puncture attempts was 1.12 (range, 1–3). The average procedure time was 13 min (range, 7–21 min).

TABLE 1 Angulation between the right EJV and SCV or AJV or TCV/SSV

Angulation type	SCV	AJV	TCV/SSV
Sharp	72 ± 28 (12)	43 ± 8 (94)	63 ± 22 (94)
Obtuse	144 ± 36 (88)	122 ± 10 (6)	135 ± 4 (6)

Note. Data are mean angulation (degree), with percentage in parenthesis.
EJV, external jugular vein; SCV, subclavian vein; AJV, anterior jugular vein; TCV, transverse cervical vein; SSV, suprascapular vein.

In eight patients (15%) where the preoperative CT-V demonstrated an EJV–SCV sharp-angle type, or an EJV–AJV obtuse-angle type or an EJV–TCV/SSV obtuse-angle type, a guide wire technique was used under fluoroscopy [10]. In six patients of EJV-SCV sharp-angle type (4 patients) and EJV–AJV obtuse-angle type (2 patients), CVC placement via EJV was obtained using a guide wire technique under fluoroscopy. In two patients (4%) of EJV–TCV/SSV obtuse-angle type, the right FV cannulations were used after the EJV cannulations have failed. In the remaining 44 patients, the catheter was inserted via the right EJV without any problem. Catheter-tip location on initial CXR was in the upper right atrium (RA) in 2 patients (4%). Fluoroscopy was used to help manipulate the central line for acceptable catheter placement. In one patient, the CT-V could not identify the left IJV, EJV, or the right EJV (Figure 3a). The Doppler color ultrasound demonstrated significantly turbulent flow with a decreased flow velocity in the left IJV (Figures 3b and c). Central venous access via the right EJV was obtained in this patient without any problem.

There were no significant procedural complications (pneumothorax, expanding hematoma, or carotid artery puncture) during the 50 catheterization attempts.

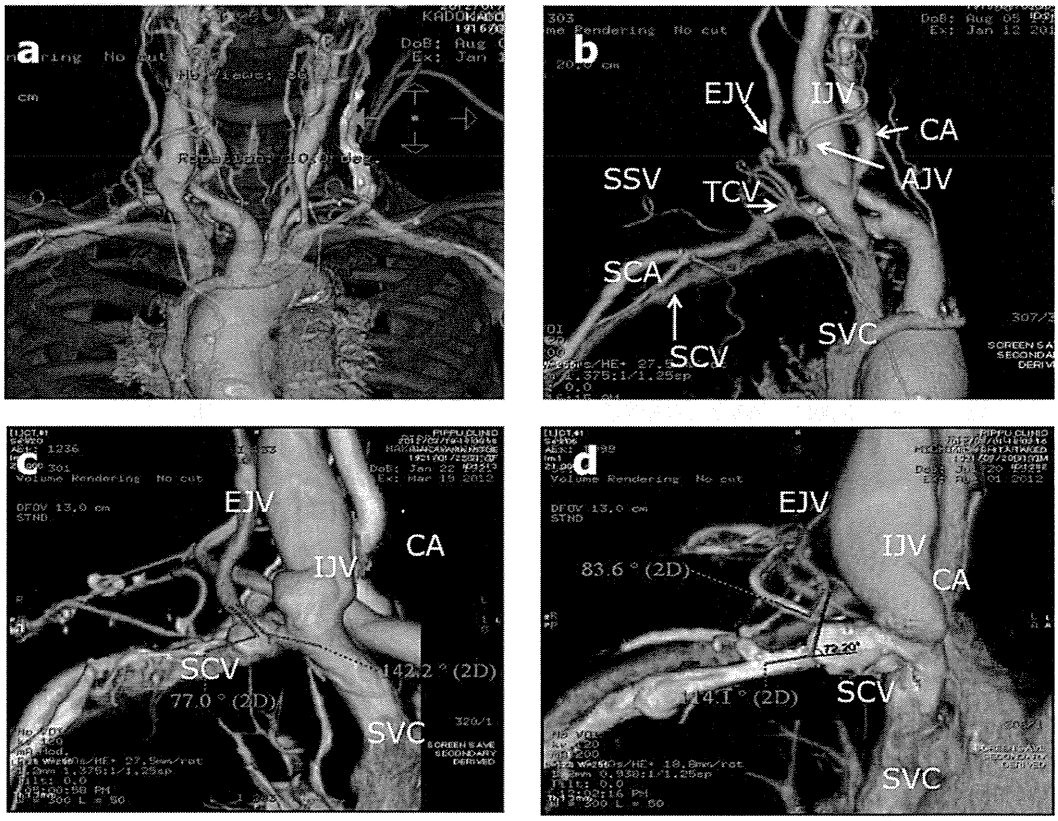

FIGURE 1 (a and b) MDCT venography of the cervical venous plexus: anteroposterior (AP) and lateral volume-rendered (VR) images. The CT-V showed a detailed cervical venous plexus and the central venous system. The CT-V clearly revealed individual vascular anatomies around the EJV and SCV junction. EJV, external jugular vein; IJV, internal jugular vein; CA, carotid artery; AJV, anterior jugular vein; TCV, transverse cervical vein; SSV, suprascapular vein; SCA, subclavian artery; SCV, subclavian vein; SVC superior vena cava; AA, aortic arch. The CT-V showed the angle between the left EJV and the SCV. The mean angulation between the right EJV and the right SCV measured 144 ± 36 degrees in the obtuse-angle cases (c) and 72 ± 28 degrees in the sharp-angle cases (d).

In three patients (6%), the small amount of subcutaneous oozing of the blood over the EJV was observed. The catheter dwell time ranged from 14 to 70 days, with a mean dwell time of 35.2 days. Catheter-related infections were observed in 2 patients (4%). No thrombotic complications were demonstrated on the clinical examination, follow-up MDCT study or ultrasonography in 50 cases during the study.

DISCUSSION

Conventional access sites include the IJV and the SCV. The former should be considered as the primary access site for all patients [11]. The incidence of technical complications associated with SCV insertion is high [2, 4–6]. The major complications of central venous catheterization may prove to be serious, particularly in critically ill patients. When the right IJV is not available for CVC, the second access site remains variable. Before utilization of the SCV, the EJV should be used [4, 7]. The benefits inherent in the use of the EJV include its large size and a greater ability to accommodate larger or multilumen catheters more easily than many peripheral insertion sites, the superficial location, the ability to visualize the EJV and the ease of access in reaching the SVC. The technique of central venous catheterization via the EJV was reported in 1974 [10]. The EJV approach has not been popular because of its low success rate [16], which is due to further anatomical considerations. The temporal and occipital veins drain into to EJV. The EJV flows in a curved and nonfixed course through the neck from the angle of the mandible obliquely to the base of the neck. At lower segments of the EJV, the AJV, TCV, and SSV drain to the EJV at the entrance to SCV, the EJV runs in a lateral direction, potentially leading to the arm rather than the thorax. In approximately 4% of the population, there is a plexus of veins under the clavicle [17]. Variations of these veins at the terminal point and angulation of the EJV to the SCV contribute to the insertion failure rate [10]. The EJV has two sets of valves, one at the entrance to the SCV and the other located 4 cm above the clavicle. These conditions cause difficulty in withdrawing catheters that have become kinked or

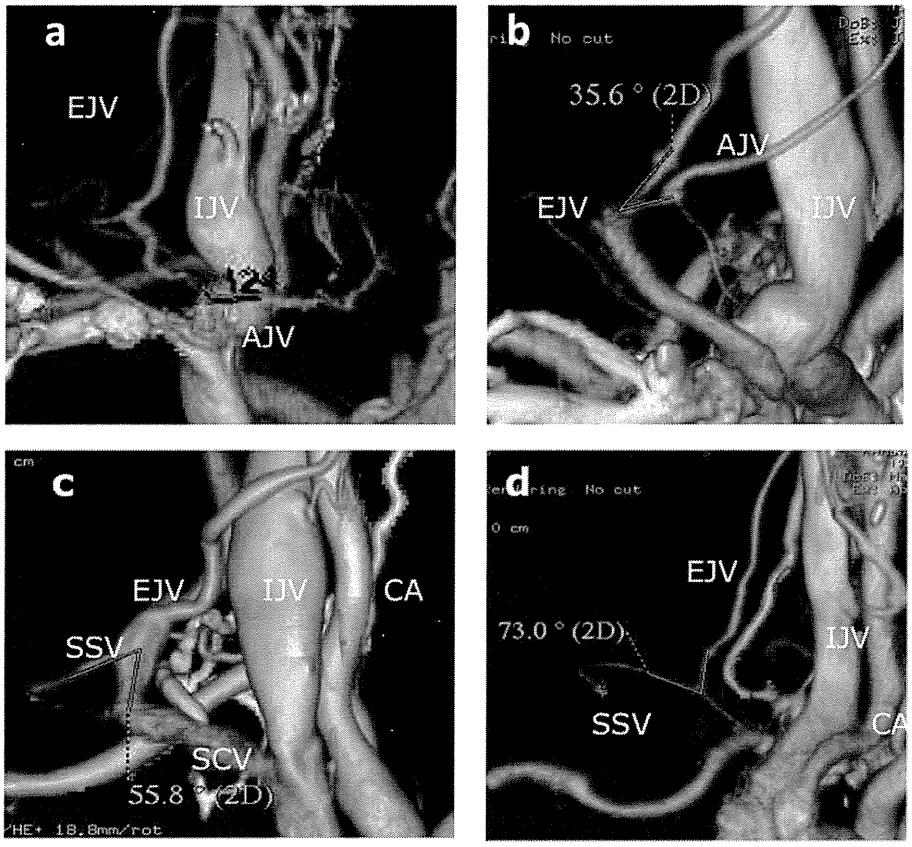

FIGURE 2 (a–d) MDCT venography: AP VR images. The CT-V showed the sharp angulation between the EJV and the AJV (a), and the EJV–AJV obtuse type (b). The sharp anglulation between the EJV and the SSV/TCV (c), and the EJV-TCV/SSC obtuse type (d).

knotted in the EJV [18]. Catheterization from the EJV requires a detailed anatomical orientation of these vessels including the central vascular system before the insertion procedure. Three-dimensional CT-V using MDCT clearly revealed individual vascular anomalies around the EJV and the SCV junction and could play an important role in safe cannulization. In our study, the angulation between the EJV and the TCV/SSV was most responsible for insertion success. Multiple access sites may be required to identify a suitable vein for central access. The CT-V can be an excellent tool for preprocedural mapping in more difficult venous access patients (4). MDCT venography has been shown to be as accurate as digital subtraction venography in central venous mapping [19, 20]. In some cases, the major problem encountered in threading an intravenous catheter through the EJV into the SCV without using a guide wire is the inability to pass the venous valve and the acute angles of tortuous veins. The J-wire easily transverses tortuous vessels, slides past valves, and navigates sharp angles [11]. When compared with the IJV or SCV sites, the EJV site offers a small risk of bleeding, puncture of the carotid artery, or pneumothorax in frail, elderly patients [10, 11, 21–24]. In this study, CT-V could not identify the left IJV, the EJV, or the right EJV in one case. The Doppler color ultrasound demonstrated significantly turbulent flow with decreased flow velocity of the left IJV. We could find this problem, which might cause complications with preoperative CT-V. Before utilization of the opposite side of IJV, the EJV should be used after the accurate estimation of condition of those vessels. Our results demonstrate percutaneous EJV cannulation to be safe for central venous access, with a high success rate compared with other sites [10, 11, 24]. However, it should be noted that the superficial location of the EJV and the small amount of subcutaneous tissue over the EJV may lead oozing of the blood. A short time simple manual compression can control subcutaneous oozing [11]. Superficial hematoma was the only problem found with the EJV route, and it was observed most often in the failed attempts. The site for percutaneously inserted catheters is determined by multiple factors, including the clinical status of patients, the purpose of central access, anticipated length of time it will be needed, and physician experience [25]. However, because of its high cost (CT-V cost: $238) and limited availability, the described procedure is not yet used for the routine diagnosis of venous