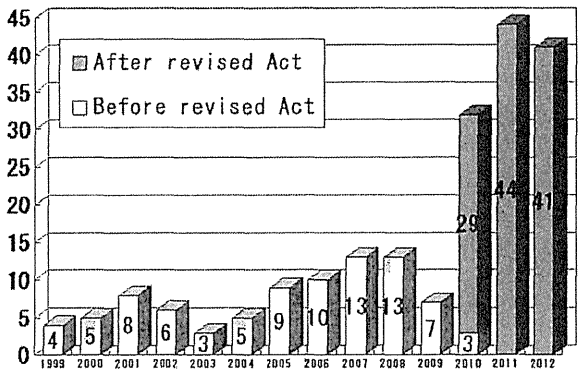

Fig 1. Brain-dead organ donation in Japan.

The most troublesome issue facing transplantation is primary graft dysfunction (PGD). This complication is the leading cause of death in the first 30 days and first year post-transplantation worldwide.[1] The use of marginal donor organs may increase the rate of PGD. From this point of view, it is necessary to establish a special evaluation and management system to maximize cardiac and lung donor utilization. The purpose of this study was to review Japanese special strategies to identify and manage, 200 BD organ donors since issuance of the Japanese Organ Transplantation Law.

MATERIALS AND METHODS

We retrospectively reviewed all 200 brain-dead donors procured in Japan between October 17, 1997, and November 14 2010, including 118 males and 78 females with an overall mean age of 45.1 years. The cause of brain death was cerebral stroke (n = 119: subarachnoid hemorrhage, 7 cerebral infarction, and 21 intracerebral bleeding), head trauma (n = 37), asphyxia (n = 27) and brain injury after cardiopulmonary resuscitation (n = 17).

Medical Consultant System to Evaluate and Manage BD Organ Donors

Since BD organ transplantation was started on February 28, 1999, every organ procurement team has obtained a staff physician in each procurement hospital. Before the procurement operation they evaluate the condition of the donor organs by ultrasound examinations of the heart and abdomen and bronchofiberscope (BFS) candidates in the intensive care unit (ICU).[4]

Since November 2002, special transplant management doctors (medical consultants [MC]) who were usually cardiac transplant surgeons, have been sent to the procurement hospital. They assessed donor organ function to identify organs useful for transplantation. They also intensively care for the donor, stabilize the donor hemodynamics by giving antidiuretic hormone (ADH) as a bolus infusion (0.01 U/kg) followed by a drip infusion (0.01 U/kg/h) and reduce the doses of intravenous catecholamines as much as possible, and seek to improve donor cardiac and lung function by preventing and treating infection before the procurement teams arrive at the donor hospital.

Since the 50th BD donor in December 2006, we have modified lung management. Regular toilet and turning of the donor were done as previously. If there were symptoms and/or signs of atelectasis or pneumonia on chest X-ray and chest computed tomography (CT) scan, repeated we perform BFS and frequent toileting. Since 2011, lung transplant surgeons have played a role in evaluation and management of the lungs. Currently the MCs consist of about 20 cardiac, 30 lung, and 3 liver transplant surgeons.

Current Organ Donor Evaluation System in Japan

First step: donor evaluation. Transplant procurement coordinators (PTC) of Japan Organ Tx Network (JOT) are called to a donor hospital if there is a potential BD donor. They obtain the patient's clinical course from the medical staff and examine clinical records to determine whether the patient is suitable for organ donation. If there are no absolute contraindications, such as an untreated malignancy or severe viral infection, they obtain informed consent for donation from the family. Then a legal examination for BD is performed.

Second step: donor evaluation. After completion of the initial clinical examination, MCs are sent to the hospital. They and the JOT PTC check the clinical records of the course before and after BD, medication review, blood examination, electrocardiogram, chest X-ray, abdominal and chest CT scans, and perform ultrasound examinations of the heart, liver, pancreas, and kidneys as well as a BFS. MCs rule out malignancies from the CT scan and ultrasound examination. JOT PTCs construct donor evaluation sheets which are sent to transplant centers using a mobile system. Then the transplant centers decided whether their recipient is suitable and their procurement team is sent to the hospital.

Third step: donor evaluation. After arriving at the donor hospital, they also evaluate the condition of donor organs by ultrasound examinations for the heart and abdominal organs and BFS by themselves in the ICU before the procurement operation.[4] They assess organ function to determine whether the organ could be transplanted to their recipient.

Final donor evaluation. After opening the chest and abdomen, the procurement team evaluates organs by watching and touching carefully. Usually a liver biopsy is performed to exclude more than moderate grade fatty liver and malignancies. They also rule out unexpected malignancies in the pleural and abdominal cavities.

Preprocurement Meeting and Management of Procurement Operation

Before starting the procurement operation, surgeons, anesthesiologists and operating room nurses gather in a meeting room. They negotiate the types of procured organs, how to procure each organ (eg, organ dissection/perfusion technique, incision lines, blood drainage technique, etc), the kinds of samples needed (eg, blood, lymphnodes and spleen), and how to manage the donor during the operation.

As most Japanese anesthesiologists have never experienced a procurement operation from a BD donor, MC also support them to stabilize donor hemodynamics during the operation. Skillful staff, not resident surgeons, harvest the donor organ.

As an inverse relationship between volume of intraoperative colloid and early lung allograft function has been reported,[5] packed red blood cells and albumin was transfused to maintain circulating blood volume and to replace proteins and fluids during the procurement operation. To improve organ perfusion with preservation solution, catecholamines are not additionally administered seeking to dilate the vessels to organs; the ADH and catecholamine infusions are discontinued at the time of the bolus infusion of heparin sulfate (400 U/kg).

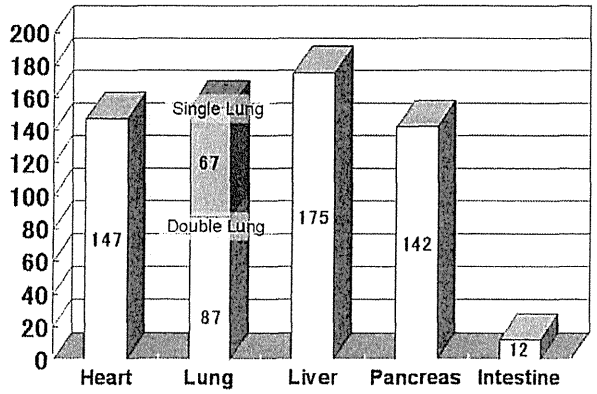

Fig 2. Organs transplanted from 200 brain-dead donors.

RESULTS

We performed 146 heart, 1 heart-lung, and 154 lung (87 single and 67 bilateral), 175 liver (28 split liver), 142 pancreas (114 pancreas-kidney), 253 kidney, and 12 small bowel transplantations (Fig 2). Although donor age has increased after the revision of the Act, the number of organs transplanted per donor and patients transplanted per donor were around 5 and 4 respectively (Fig 3). Patient survivals at 5 and 10 years are shown in Table 1.

DISCUSSION

For many years, "traditional criteria" have been used to identify an appropriate transplant donor. However, over the past 2 decades, there has been a considerable increase in the numbers of patients listed annually for organ transplantation. Strict adherence to standard donor criteria has resulted in a progredient undersupply of available organs with significantly extended waiting times and increased waiting list mortality.[2,6]

Table 1. Patient Survival After Organ Transplantation

	Heart	Lung	Liver	Pancreas
5-y survival rate (%)	95.2	72.7	78.6	76.0
10-y survival rate (%)	95.2	54.0	70.8	62.6

As a consequence of this severe shortage of donor organs, marginal donors have been utilized in many countries. However, only 2407 hearts of 7944 deceased donors (30.2%) were transplanted in the United States in 2010. Because of the strict Japanese Organ Transplantation Law, only 200 BD donors have been procured in Japan for 13 years and 60 heart transplantation (HTx) would have been performed if the cardiac donation rate from the deceased donors was same in Japan as in the United States. These great pressures of the organ shortage had made transplant programs consider the use of organs that would be considered to be marginal. Therefore, an original donor evaluation and management system has been established in Japan, including the MC and the preprocurement meeting.[4]

High serum adrenaline concentrations, as usually observed after its administration, reduce myocardial β-adrenergic receptor density in BD animals[7] and patients,[8] which may increase the risk of primary graft dysfunction after HTx. Therefore, the intravenous catecholamine dose should be reduced as much as possible. It has been recommended as initial therapy for hemodynamic support and treatment of diabetes insipidus by the American College of Cardiology,[9–11] due to its catecholamine-sparing effects.[6,10] Repletion of vasopressin to treat diabetes insipidus to maintain hemodynamic stability and prevent electrolyte imbalance

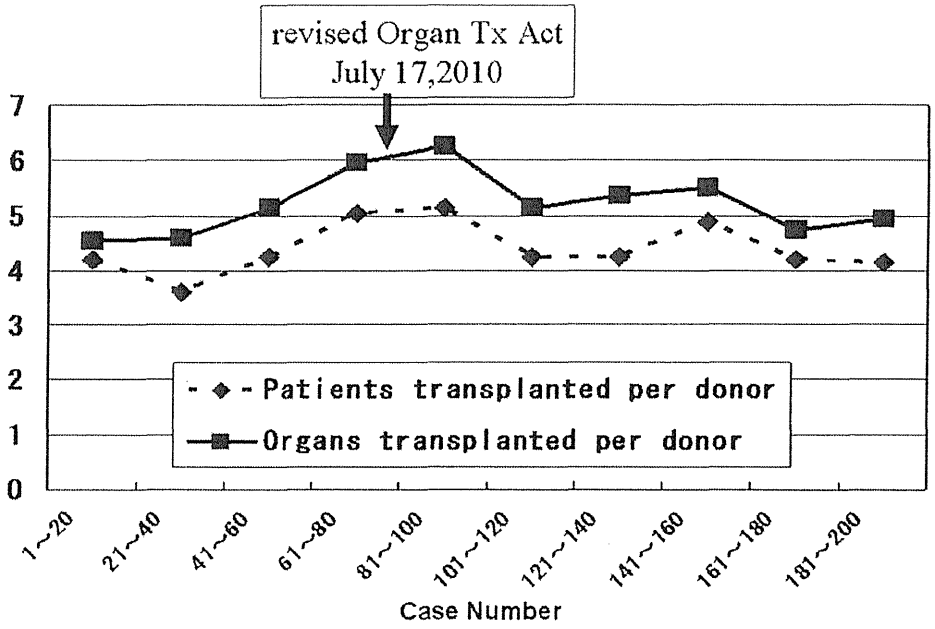

Fig 3. Patients and organs transplanted per donors.

is noncontroversial. A substantial number of BD donors resolve their focal/regional wall motion abnormalities. Aggressive attempts at hemodynamic stabilization using hormonal resuscitation have resulted in dramatic reversibility of cardiac dysfunction.[10,12]

The ideal lung donor has a PaO_2/FiO_2 ratio more than 300, positive end expiratory pressure requirement greater than 5 cm H_2O, clear chest X ray, age older than 55 years, smoking history of more than 20 packs/y, and absence of trauma, surgery, aspiration, malignancy, and purulent secretions. Pathologic studies of lungs deemed unsuitable for donation have indicated that bronchopneumonia, diffuse alveolar damage, and lung consolidation are the most common reasons to reject a lung. Given these findings, it is recommended that every lung donor undergo BFS for therapeutic bronchial toilet, and to isolate potential pathogens to guide antibiotic therapy in both the donor and the recipient.[10]

In conclusion, although the number of transplantations is still small, the availability of organs has been greater in Japan and their outcomes acceptable. The strategies presented herein may be useful to maximize organ transplant opportunities even in other countries.

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We would like to acknowledge and extend our heartfelt gratitude to many heart and lung transplant surgeons who have actually worked as a medical consultant despite of daily hard work and made the completion of this paper possible.

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ELSEVIER

Japanese Strategies to Maximize Heart and Lung Availabilities: Experience from 100 Consecutive Brain-Dead Donors

N. Fukushima, M. Ono, S. Saito, Y. Saiki, S. Kubota, Y. Tanoue, M. Minami, S. Konaka, and J. Ashikari

ABSTRACT

Objective. Because the donor shortage is extremely severe in Japan because of a strict organ transplantation law, special strategies have been established to maximize heart and lung transplantations (HTs and LTs, respectively). We reviewed 100 consecutive brain-dead donors to evaluate our strategies to identify and manage heart and lung donors.

Methods. We retrospectively reviewed all 100 consecutive brain-dead donors procured since the law was issued in 1997. There were 56 mens and the overall mean donor age was 43.5 years. The causes of death were cerebrovascular disease (n = 62), head trauma (n = 20), and asphyxia (n = 16): Since November 2002, special transplant management doctors were sent to donor hospitals to assess cardiac and lung functions, seeking to identify transplant opportunities. They stabilized donor hemodynamics and lung function by administering antidiuretic hormone intravenously and performing bronchofibroscopy for pulmonary toilet.

Results. Seventy-nine HTs, 1 heart-lung transplantations, and 78 LTs (46 single and 32 bilateral) were performed. By applying these strategies organs per donor were increased from 4.5 to 6.8. Among heart donors, 61/80 were marginal: high inotrope requirement (n = 29), cardiopulmonary resuscitation (n = 28), and/or >55 years old (n = 20). None of the 80 HT recipients died of primary graft failure (PGF). Patient survival rate at 10 years after HT was 95.4%. Among lung donors, 48/65 were marginal: pneumonia (n = 41), chest trauma (n = 4), and >55 years old (n = 9). Only 2/78 LT recipients died of PGF. Patient survival rate at 3 years after LT was 72.2%. After inducing frequent pulmonary toilet, lung procurement and patient survival rates increased significantly after LT.

Conclusions. Although the number of cases was still small, the availability of organs has been greater and the outcomes of HT/LT acceptable.

HEART AND lung transplantation (HT and LT, respectively) represent established procedures that show in satisfying long-term results for end-stage heart and respiratory failure patients.[1] However, these therapies are limited by severe donor organ shortages. Therefore, optimal utilization of all suitable donor organs is mandatory to increase graft availability.[2]

In Japan, the donor shortage has been more severe than in other developed countries because of the strict Japanese organ transplantation law issued in 1997, which requires a living person to grant written consent for organ donation after brain death. Until September 30, 2010, only 100 brain-dead donors have been procured in Japan since the law was issue.[3–6] In 2007, the cardiac donation rate per million population in Japan was only 0.08, compared with 7.3 in

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USA, 5.3 in Spain, and 0.97 in South Korea. The mean waiting times for HT and LT are extraordinary long in Japan, namely, 1,026 and 1,673 days respectively, in 2010. The organ shortage and long waiting times have forced Japanese transplant programs to consider the use of hearts and lungs from donors who would be considered to be marginal.[6]

The most troublesome issue facing transplantation is primary allograft failure (PGF). This complication is the leading cause of death in the first 30 days and in the 1 year after transplantation in the world.[1] The use of marginal donor organs seems to increase the rate of PGF. Therefore, it is necessary to establish special donor evaluation and management systems that maximize cardiac and lung donor utilization. The purpose of the present study was to review our special strategies to identify and manage heart and lung donors among 100 consecutive brain-dead donors since issuance of the Japanese organ transplantation law.

MATERIALS AND METHODS

In this study, we reviewed retrospectively 100 brain-dead donors procured in Japan from October 17, 1997, to September 30, 2010, 56 were male, and the ages of the donors range from 18 to 72 years (mean, 43.3 ys). The cause of brain death was cerebral stroke in 61, including 52 with subarachnoid hemorrhage, 5 cerebral infarctions, and 4 cerebral bleedings, head trauma in 20 including 10 motor vehicle accidents, 16 in stavces of asphyxia, and 4 of brain injury after cardiopulmonary resuscitation.

Donor Evaluation and Management System

Organ transplantation from brain-dead donors started in 1999. Since then, each organ procurement team includes staff physicians who evaluate the condition of donor heart and lungs by echocardiography and flexible bronchofibroscopy (BFS) in the intensive care unit before the procurement operation.[6] Since November 2002, a medical consultant (MC) has been sent to the procurement hospital, to also assess donor organ function and identify suitable organs for transplantation. They also intensively care for the donor, stabilizing hemodynamics by administering a bolus infusion of 0.01 U/kg followed by a drip infusion of 0.01 U/kg/h of antidiuretic hormone (ADH) and reducing intravenous catecholamine doses as much as possible. They seek to prevent or to treat lung infections before the procurement teams arrive.

If the ratio of arterial oxygen tension to inspired oxygen fraction (PaO_2-FiO_2 ratio) was <300, one lung was transplanted if the PaO_2-FiO_2 ratio of the pulmonary venous blood of that side sampled at the procurement operation was >400.

After the 50th brain dead donor in December 2006, we modified the lung management. While, regular toilet and turning of the donor were performed as previously, repeated BFS was carried out when there were symptoms and/or signs of atelectasis or pneumonia on the chest X-ray or computerized tomography (CT) scan.

We defined a marginal donor heart as one from a donor with a history of cardiopulmonary resuscitation >5 minutes, with left ventricular dysfunction defined via transthoracic echocardiography demonstrating left ventricular ejection fraction <50%, with high inotrope requirement defined as a sustained need for dopamine >10μg/kg/min, or >55 years of age.

We defined as marginal donor lung was among from a donor with infections sputa or findings of pneumonia by chest-X-ray, who is hemodynamically unstable, who sustained chest trauma, or >55 years age.

Preprocurement Meeting and Management of Procurement Operation

Before starting a procurement operation, all surgeons, anesthesiologists, operating rate and nurses gathered in the meeting room. They negotiated the types of procured organs, how to procure each organ (eg, organ dissection/perfusion technique, incision lines, blood drainage technique), needed samples (eg, blood, lymph nodes, spleen), and donor management during the operation. Because most Japanese anesthesiologists have never experienced a procurement operation from a brain-dead donor. The MC also supported them to stabilize donor hemodynamics during the operation. Skillful staff surgeons, not resident surgeons, harvested the donor organs.

Because an inverse relationship between volume of intraoperative colloid and early lung allograft function has been reported,[7] packed red blood cells and albumin were transfused to maintain the circulating blood volume and to replace proteins and fluids. To improve organ perfusion with preservation solution, additional catecholamine was not administered (as possible to dilate the vessels of organs). ADH and all catecholamine infusions were discontinued at the time of the heparin sulfate (400 U/kg) bolus.

RESULTS

Among 100 brain-dead donors, we obtained 79 HTs (80.0%), 78 LTs (32 bilateral and 46 single) from 65 donors (58.7%), and 1 heart and lung transplantations (HLT).

Heart Transplantation

Seventy-nine HTs were performed at 7 centers, 58 of them male. The overall age of the HT recipients was 8–60 years (means 36.7 ys). Their underlying diseases were dilated cardiomyopathy (DCM; $n = 60$), dilated hypertrophic cardiomyopathy ($n = 6$), ischemic cardiomyopathy ($n = 6$), secondary DCM ($n = 5$), restrictive cardiomyopathy (RCM; $n = 1$), and in complex cardiac anomaly ($n = 1$). All patients were transplanted under status 1 hemodynamic condition with 69 requiring left ventricular assist support for a mean duration of 821 days (range 21, 1,593). The mean waiting period for HT was 950 days (range 29, 2,595).

Among 79 HTs, 61 donors were marginal including 35 treated with high-dose catecholamines, 4 with <50% left ventricular ejection fraction, 29 with history of cardiopulmonary resuscitation, and 9 > 55 years old without coronary angiography.

Although 3 patients required mechanical support (2 for extracorporeal membrane oxygenation and 1 for intraaortic balloon pumping) and 2 required high dose inotropic support, none of the 79 HT recipients died from PGF. Two succumbed to infections at 3 months and 4 years after HT. Patient survivals at 1, 5, and 10 years after HT were 98.7%, 96.2%, and 96.2%, respectively (Fig 1).

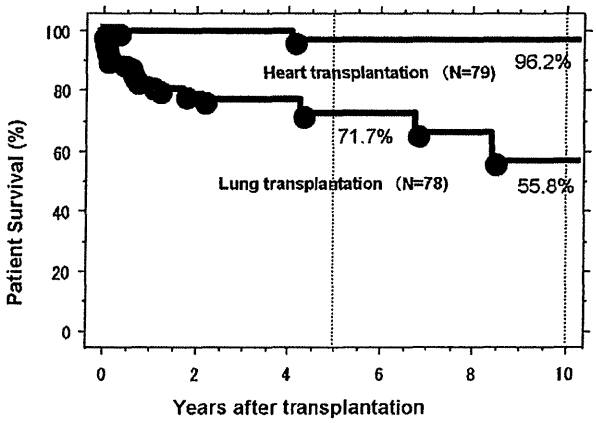

Fig 1. Patient survival after heart and lung transplantation.

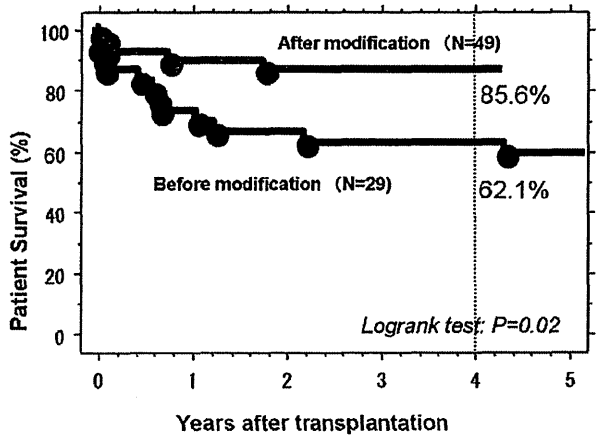

Fig 2. Patient survival after lung transplantation before and after modification of donor management.

Lung Transplantation

The 78 LTs included 32 bilateral (BLT) and 46 single (SLT) LTs at 7 centers, the in of 29 men. The overall age/range of the LT recipients was 19–60 years (mean, 38.3 ys). The underlying disease for LT was lymphangioleiomyomatosis (LAM; n = 28) primary pulmonary hypertension (n = 16), idiopathic or other interstitial pneumonia (n = 14), bronchiolitis obliterans (n = 4), Eisenmenger syndrome (n = 3; ventricular septal defect, 1 partial pulmonary venous anomalous drainage, and 1 patent ductus arteriosus), emphysem (n = 6), bronchoectasia (n = 3), or another reasons (n = 3). The waiting period for LT was 22–2,345 days (mean, 1,056 ds).

Among 65 lung donors, 48 were considered to be marginal including 32 due to infectes sputa or pneumonia by chest-X-ray or CT scan. There were 7 hemodynamically unstable donors, and 6 had experienced chest trauma. Nine were >55 years old.

Among the 8 recipients who, died early after LT, 4 succumbed due to PGF, 2 due to technical reasons, and 2 due to sepsis. Patient survivals at 1, 5, and 10 years after LT were 82.5%, 71.7%, and 55.8 %, respectively (Fig 1). The 1 HLT performed for Eisenmenger syndrome associated with double-outlet right ventricle, was alive after 2 years.

After the 50th brain dead donor, lungs management was modified as described above. Before modifying lung management, 29 LTs (13 SLTs and 16 BLTs) were performed from 27 donors. After modifying lung management, 49 LTs (33 SLTs and 16 BLTs) were performed from 38 donors. Lung procurement rate per donor significantly increased to 74.5% from 55.1% after the modification (Pearson, chi-square test: P = .04). However, there was no difference in the rate of early death after LT due to PGF and other causes. Patient survival at 1, 2, and 4 years after LT significantly increased after the modifications from 89.1%, 85.8%, and 85.8% before to 72.4%, 65.5%, and 62.1% respectively, after modification, (log rank test: P = .02; Fig 2).

DISCUSSION

For many years, HT and LT have represented established procedures for end-stage heart and respiratory failure patients. Over the past 2 decades, there has been a considerable increase in the numbers of patients annually listed for these procedures. Strict adherence to "standard donor criteria" resulted in a undersupply of available organs with the result of significantly extending waiting times and increasing waiting list mortality.[2,8]

As a consequence of this severe shortage of donor organs, hearts and lungs from marginal donors have been utilized in many countries. However, only 2,407 hearts from 7,944 deceased donors (30.2%) were transplanted in the USA in 2010. Because of the strict Japanese organ transplantation law only 100 brain-dead donors have been procured in Japan in >10 years. Only 30 HTs would have been transplanted, if the cardiac donation rate was the same as in the USA. These great pressures of the organ shortage made transplant programs consider the use of the hearts and lungs that would be considered to be marginal. Therefore, original donor evaluation and management systems have been established, such as the MC and the preprocurement meeting.[6]

High serum adrenaline concentrations have been reported to reduce myocardial β-adrenergic receptor density in brain dead nonhuman animals[9] and human patients.[10] These concentrations can increase the risk of PGF after HT. Therefore, the dose of intravenous catecholamine should be reduced as much as possible. The American College of Cardiology has recommended it as the initial therapy for hemodynamic support after failure of treatment of diabetes insipidus,[11–13] which shows catecholamine-sparing effects.[6,14] Vasopressin replacement treats diabetes insipidus as well as maintains hemodynamic stability and prevents electrolyte imbalance. A substantial number of brain-dead donors show resolution of their focal/regional wall motion abnormalities. Aggressive attempts at hemodynamic stabilization with the use of hormonal resuscitation

have dramatically improve reversed cardiac function and yield.[12,14]

The ideal lung donor shows a PaO_2-FiO_2 ratio of >300, a positive end-expiratory pressure requirement >5 cm H_2O, a clear chest X-ray, age >55 years, a smoking history of >20 packs/year, and absence of trauma, surgery, aspiration, malignancy, and purulent secretions. Pathologic studies of lungs deemed to be unsuitable for donation have indicated that bronchopneumonia, diffuse alveolar damage, and lung consolidation are the most common reasons to reject a lung. Given these findings, it is recommended that every lung donor undergo bronchoscopy for a therapeutic toilet and to isolate potential pathogens to guide antibiotic therapy in both the donor and the recipient.[12]

In the present study, after modifying lung management, lungs procured per donor significantly increased and, moreover, with significantly increased patient survival.

In conclusion, although the number of transplantations is still small, the availability of hearts and lungs has been greater in Japan than in other developed countries the outcomes of HT and LT were acceptable. These strategies may be useful to maximize HT and LT opportunities in other countries.

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ORIGINAL ARTICLE

Life-threatening risk factors and the role of intestinal transplantation in patients with intestinal failure

Motoshi Wada · Kotaro Nishi · Megumi Nakamura · Hironori Kudo · Satoshi Yamaki · Hideyuki Sasaki · Tomoyuki Sato · Taichi Fukuzawa · Hiromu Tanaka · Takuro Kazama · Shintaro Amae · Masaki Nio

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Abstract
Purpose We elucidated the life-threatening risk factors for intestinal failure (IF) and characterized the role of intestinal transplantation (ITx) in affected patients.
Methods We conducted a retrospective review of 38 patients with short bowel (SB) and 19 with motility disorders (MD). The SB patients were divided into three categories according to the length of their residual small bowel and the presence of the ileocecal valve. The four disease subcategories were grouped into two categories: low-risk category (mild and moderated SB) and high-risk category (extensive SB and MD). The age at the introduction of parenteral nutrition (PN) was <1 year in 50 patients (infant group, IG) and 1–15 years in 7 patients (pediatric group, PG).
Results Enteral autonomy was rarely achieved in the high-risk category ($p < 0.0001$). IG was associated with a higher incidence of developing intestinal failure-associated liver disease (IFALD) ($p = 0.004$). Eight patients died, due to IFALD in four, sepsis in three and acute heart failure in one. Twenty-eight patients (49 %) are currently alive without PN, including four after ITx.
Conclusion The treatment of high-risk IF is still challenging. Inclusion of ITx in appropriate timing, along with aggressive medical, nutritional and surgical management, may reduce advanced morbidity and mortality of high-risk IF.

Keywords Intestinal failure · Intestinal rehabilitation · Intestinal transplantation · Intestinal failure-associated liver disease

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Introduction

Intestinal failure (IF), a critical condition caused by the reduction of the bowel in length or function below the minimum requirements for adequate digestion and absorption of nutrients to maintain healthy growth in children, has been associated with high morbidity and mortality rates, because children with IF are at an especially high risk of developing intestinal failure-associated liver disease (IFALD).

The outcomes of children with IF have evolved dramatically in the past decade. Both recognition of the need for individualized, multidisciplinary, medical and/or surgical management of children with severe IF and the recent advances in the outcomes of intestinal transplantation (ITx) have contributed to the improvements [1, 2]. In addition, intestinal rehabilitation programs (IRP) have been established in some specialized institutions with the aim of providing better care for such patients [3, 4]. Our institution is one of the few centers with established IRP and ITx programs in Japan.

In this study, we assessed the outcomes of the treatment for IF patients and elucidated the life-threatening risk

factors in the patients to characterize the possible roles of ITx under the current IRP.

Methods

We conducted a retrospective review of all patients with IF treated at our institution. From 1978 to 2012, a total of 62 patients were treated for IF and/or referred to be considered for ITx at our institute. After excluding one adult transplant patient in whom PN was introduced after the age of 15 years, and four children who died for reasons unrelated to IF, 57 children (33 males and 24 females) were enrolled in this study.

IF is defined as a residual small bowel (RB) length of less than 40 cm or a requirement for parenteral nutrition (PN) support for more than 42 consecutive days [3] and IFALD is defined as hyperbilirubinemia in which the direct bilirubin concentration is higher than 2.0 mg/dL for more than 2 months. IF usually develops when the RB is less than 20–33 % of the total small intestine length sufficient to absorb nutrients where the normal total small intestinal length is 1.5 ~ 2.0 m in neonate/infant, 2.0–4.0 m in child, and 4.0–6.0 m in adult [5].

The primary underlying diseases associated with IF were intestinal volvulus ($n = 19$, 33 %), congenital intestinal atresia ($n = 12$, 21 %), gastroschisis ($n = 4$, 7 %), necrotizing enterocolitis ($n = 2$, 4 %), extensive aganglionosis ($n = 6$, 10 %), hypoganglionosis ($n = 7$, 12 %), chronic idiopathic intestinal pseudo-obstruction syndrome (CIIPS, $n = 2$, 4 %), megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS, $n = 2$, 4 %) and other single or combinations of diagnoses ($n = 3$, 5 %).

These children were first divided into two disease categories: 38 (21 males and 17 females) with short bowel (SB) and 19 (12 males and 7 females) with motility disorders (MD). The SB patients were divided into three subcategories according to the length of their RB and the presence of the ileocecal valve (ICV): category A (mild SB, $n = 18$), RB $\geq$ 40 cm; B (moderate SB, $n = 8$) RB < 40 cm with the ICV and C (extensive SB, $n = 12$) RB < 40 cm without the ICV. These four disease subcategories were grouped into two risk categories: a low-risk category (mild and moderate SB) and a high-risk category (extensive SB and MD). The age at the time of the introduction of PN was <1 year in 50 patients (infant group, IG) and 1–15 years in 7 patients (pediatric group, PG). The median age at the time of this study of the IG and PG patients were 11.4 (0.6–44.5) and 25.1 (7.5–39.7) years, respectively.

Outcomes such as the mortality rate, dependence on PN, development of IFALD and need for ITx were assessed and compared between the age groups and the risk categories. The statistical analyses were performed using the Fisher's exact probability test for the comparisons. A significant difference was defined as $p < 0.05$.

This study was conducted with institutional ethics board approval.

Results

Weaning from PN without ITx was achieved at a significantly higher rate in the low-risk category patients (23/26, 88 %) than in the high-risk category (1/31, 3 %, $p < 0.0001$) (Table 1). The median duration of PN was 7 months (range, 2–29 months) in patients who finally achieved enteral autonomy. The incidence of weaning from PN without ITx was not significantly different between the IG and PG patients ($p > 0.9999$).

IFALD developed in 7 of 18 (38 %) patients in category A, 4 of 8 (50 %) in category B and 6 of 12 (50 %) in category C in the SB patients and 12 of 19 (63 %) in the MD patients (Table 2). There were no significant differences in the development of IFALD between the risk categories ($p = 0.29$). IFALD developed at a significantly higher rate in the IG (29 of 50 patients, 58 %) compared with the PG (0 of 7, 0 %) patients ($p = 0.004$).

Among the 29 IG children who developed IFALD, 3 of 6 infants with extensive SB and 1 of 12 MD died of IFALD at a median age of 10 months (range, 7–31 months). A total of eight patients died, the four described above, three

Table 1 Incidences of achieving enteral autonomy without intestinal transplantation (ITx)

Disease category	SB			MD	Subtotal	
Subcategory	A	B	C			
Risk category	Low		High			
IG (Infant Group)	16/16	4/7	0/9	1/18	21/50	P>.9999
PG (Pediatric Group)	2/2	1/1	0/3	0/1	3/7	
Subtotal	23/26		1/31		24/57	
	P<.0001					

Table 2 Incidences of developing intestinal failure-associated liver disease (IFALD)

Disease category	SB			MD	Subtotal	
Subcategory	A	B	C			
Risk category	Low		High			
IG (Infant Group)	7/16	4/7	6/9	12/18	29/50	P=.004
PG (Pediatric Group)	0/2	0/1	0/3	0/1	0/7	
Subtotal	11/26		18/31		29/57	
	P=.29					

from sepsis and the remaining child died of acute heart failure due to selenium deficiency (Table 3). The three patients who died of sepsis had MD. The mortality rate was significantly higher in the high-risk category patients (26 %) than in the low-risk patients (0 %, $p = 0.006$). The overall survival rate was 86 % (49/57).

Seven patients (two extensive SB and five MD) received nine intestinal grafts at the median age of 27 years (range, 10–35 years). Six patients underwent isolated ITx and one 10-year-old child with IFALD required serial ITx after living-related liver transplantation. The transplantation rate was also significantly higher in the high-risk category (23 %) than in the low-risk patients (0 %, $p = 0.013$). The indications for ITx were recurrent catheter-related sepsis in four, IFALD in two, and a severe metabolic disorder in one patient. Six of the seven transplant patients had occlusions of their central venous access (Table 4). Six patients were alive (the current age of the transplant patients ranged from 12–36 years), and one died of sepsis after ITx. Two extensive SB patients (current age: 6 and 13 years old) and one MD patient (20 years of age) were still on the waiting list for ITx.

Of the 49 patients alive of the writing of this manuscript, 28 (57 %) were without the need for PN, including 4 after ITx, and the remaining 21 (43 %) were still dependent on PN.

Table 3 Mortality rates

Disease category	SB			MD	Subtotal	
Subcategory	A	B	C			
Risk category	Low		High			
IG (Infant Group)	0/16	0/7	3/9 *	5/18 **	8/50	P=.58
PG (Pediatric Group)	0/2	0/1	0/3	0/1	0/7	
Subtotal	0/26		8/31		8/57	

P=.006

* Cause of death in 3 infantile extensive SB was liver failure

** Causes of deaths in infantile MD were sepsis in 3 (one after ITx), liver failure in 1 and heart failure due to selenium deficiency in 1

Table 4 Transplantation rates

Disease category	SB			MD	Subtotal	
Subcategory	A	B	C			
Risk category	Low		High			
IG (Infant Group)	0/16	0/7	1/9 *	4/18	5/50	P>.999
PG (Pediatric Group)	0/2	0/1	1/3	1/1	2/7	
Subtotal	0/26		7/31		7/57	

P=.013

* One extensive SB child required staged liver-intestinal transplantation due to end stage liver failure

Discussion

In our present study, weaning from PN was very rarely achieved in the patients in the high-risk category (extensive SB and MD). The patients in the high-risk category endured long-term PN and frequently developed life-threatening morbidities, and eventually were indicated for ITx. We believe that aggressive IRP should be applied for such patients to decrease their mortality and improve their quality of life.

A clinical ITx program was started at our institute in November 2003. Subsequently, we also introduced aggressive enteral therapies for severe IF, such as the administration of a fish-oil-based lipid emulsion (FOLE) for IFALD, ethanol locking of the central venous catheter to prevent catheter-related infections and serial transverse enteroplasty (STEP) for extensive SB, along with conventional standard approaches.

IFALD is the most significant life-threatening complication, especially for small children with IF. The present study showed that IFALD develops exclusively in the IG patients. They were mostly congenital or neonatal IF patients in whom PN was introduced before the age of 1 month. This finding is compatible with recent reports regarding pediatric IF and IFALD [6].

The impact of intravenous lipid infusions on the development and progression of IFALD has been recently studied, and some studies have shown promising results for the prevention/treatment of IFALD using FOLE [6, 7]. Since 2009, we have successfully treated 10 children with IFALD by administering FOLE. Since we earnestly introduced using FOLE, we have not experienced any patient deaths due to IFALD. As FOLE therapy for IFALD is still limited to investigational use in Japan, the official pharmaceutical approval of FOLE by the Ministry of Health, Labour and Welfare is needed as soon as possible, and clinical trials to confirm the efficacy of this treatment are expected in the very near future.

A catheter-related bloodstream infection (CRBSI) is also a major cause of death in IF patients. In our present study, all CRBSI-related deaths occurred in patients with MD, who are possibly at a higher risk of bacterial translocation from their immotile bowel. Two MD children died of sepsis before 2003, and one patient recently died after ITx due to sepsis from partial necrosis of the intestinal graft. The incidence of CRBSI seems to have been reduced after we routinely started performing ethanol locks of the catheter for the prevention of CRBSI, although we could not statistically confirm this finding due to the limited data available regarding CRBSI.

Under the current IRP, ITx is indicated only for severe irreversible IF associated with life-threatening complications [8]. In cases where a patient with severe IF develops

irreversible liver failure due to IFALD, liver-intestine or multivisceral transplantation is indicated in Western countries [1, 2]. In contrast, even after a revision of the Organ Transplant Law in July 2010 allowed for organ donation from pediatric cadaveric donors, and despite the fact that the number of the organ donations from adult cadaveric donors has recently increased after the revision, composite grafts from pediatric cadaveric donors are still rarely available in Japan. For this reason, pediatric IRP for the prevention of IFALD is very important especially in Japan.

Between November 2003 and December 2012, we performed 10 ITx for eight patients with severe IF (including one adult patient who was not enrolled in this study). The patient and graft survival after ITx were 87.5 and 70 %, respectively, with a follow-up period of 15–109 months (median 57 months). Five patients, including one extensive SB child who had serial ITx after liver transplantation, have achieved long-term enteral autonomy after ITx. With novel immunosuppressive protocols and modern postoperative management, the short-term outcome of ITx has significantly improved in the past decades, such that the patient survival after ITx is currently similar to that after isolated liver transplantation (>80 % 1 year after transplantation) [7]. Despite this trend toward improvements in the short-term results, the long-term outcome of ITx has not yet been satisfactory. ITx would be more widely applied for severe irreversible IF if the long-term therapeutic efficacy of ITx could be confirmed, based on continual improvements in the patient outcomes.

A multidisciplinary team and a protocol-driven management algorithm for the care of IF patients have not yet been formally established, and have only recently been organized in our institute. The number of severe IF patients referred needing intensive care has been increasing. Despite the increase of high-risk IF patients and the poorer status of the patients referred to our institution, our treatment outcomes have dramatically improved since 2003, although proper chronological comparison of the outcomes before and after we introduced IRP are difficult to conduct due to the potential bias related to the limited follow-up periods of our current series of IRP. Both aggressive medical and/or surgical therapies and the introduction of ITx at an appropriate time seem to have contributed to these improvements.

The treatment of severe IF, such as infantile and/or high-risk IF, is still challenging, and is associated with high risks of the patients needing long-term PN, developing life-threatening complications and requiring extensive medical and/or surgical support. The long-term survival of patients with severe IF has recently become possible due to the current IRP. With the recent improvements in the treatment outcomes, the inclusion of ITx, provided in combination with aggressive IRP, has contributed to decreasing the mortality and improving the quality of life for patients with most severe type of IF. Therefore, referral in appropriate timing of those patients with high-risk (irreversible) IF to specialized IRP/ITx centers before the development of advanced complications is recommended [2].

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ELSEVIER

Conversion to Prolonged-Release Tacrolimus for Pediatric Living Related Donor Liver Transplant Recipients

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ABSTRACT

Prolonged-release tacrolimus allows for once-daily dosing. Although many adult recipients have been switched from standard tacrolimus, prolonged-release tacrolimus has not been popular for pediatric patients despite the potential benefits for medication compliance. We report on prolonged-release tacrolimus for 11 pediatric living related donor liver transplant (LRDLT) recipients. Patients under 18 years of age who were receiving standard tacrolimus-based immunosuppression and steroid taper underwent conversion from standard to prolonged-release tacrolimus. We monitored tacrolimus trough levels and liver function tests (LFTs). We also assessed adverse effects and satisfaction levels for prolonged-release tacrolimus. Mean age at transplantation was 4.3 years. The mean duration of follow-up was 12 months. The ratios of trough levels with prolonged-release vs standard tacrolimus were 0.97, 0.95, and 0.92 at 1, 2, and 4 weeks post conversion, respectively. Two patients discontinued prolonged-release tacrolimus owing to abnormal LFTs and neurological abnormalities, respectively; but symptoms resolved after reconversion. One patient returned to standard tacrolimus and the other was converted to cyclosporine. Once-daily administration satisfied 89% of patients. In the overall assessment, conversion to prolonged-release tacrolimus satisfied all patients. Prolonged-release tacrolimus was useful for pediatric patients after LRDLT. Trough levels after conversion were compatible with those before conversion. Most patients were satisfied with prolonged-release tacrolimus. However, some patients failed conversion because of unexpected responses. Close observation after conversion is required even if patients have previously had an uneventful course on standard tacrolimus.

PROLONGED-RELEASE tacrolimus, which is now commercially available, allows for once-daily dosing. It is widely used in adults; however, the new formulation is currently not popular for pediatric patients. Immunosuppression can be withdrawn in some pediatric patients after living related donor liver transplantation (LRDLT), but most subjects require life-long immunosuppression. Once-daily administration is potentially beneficial in terms of medication compliance for pediatric patients. Herein we have reported on prolonged-release tacrolimus in pediatric patients after LRDLT.

MATERIALS AND METHODS

Patients who were less than 18 years old at the time of conversion and who underwent LRDLT at our institution were included in this study. They had originally received the standard tacrolimus formulation with a steroid taper. Our tacrolimus taper was a target tacrolimus trough level of 10–15 ng/mL for the first month after transplantation; 5–10 ng/mL for 1 year, and 3–5 ng/mL thereafter. Steroids were administered to all patients. Patients received a bolus dose of methylprednisolone (20 mg/kg) at the time of transplantation, and were tapered off by 4 months thereafter. Prednisolone was continued for patients who had an episode of biopsy-proven acute cellular rejection or posttransplant hepatitis. Mycophenolate mofetil was administered to selected patients who experienced a steroid-resistant acute

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cellular rejection episode proven by another biopsy following steroid therapy. No patients were withdrawn from immunosuppressive therapy.

Prolonged-release tacrolimus at twice the dose of standard tacrolimus was given in the morning immediately before the switch. All subsequent prolonged-release doses were taken daily in the morning. Because once-daily prolonged-release tacrolimus was only available in capsule form, capsules were prescribed even if patients had taken the granule form of standard tacrolimus.

Blood samples to measure tacrolimus trough levels were taken just before the morning dose of prolonged-release or standard tacrolimus. Trough levels were measured 12 hours after the previous standard tacrolimus dose; prolonged-release tacrolimus levels were measured 24 hours after the previous dose. Samples were collected in the clinic at 1, 2, and 4 weeks following conversion. Whole blood samples were placed in tubes containing EDTA and stored at 4°C. Concentrations were measured within 4 hours using the Architect i2000 (Abbott Laboratories).

Serum aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGTP), and total bilirubin levels were measured concurrently with the tacrolimus trough levels. We assessed adverse effects of prolonged-release tacrolimus and levels of patient and parent satisfaction.

Data were analyzed using the JMP Ver. 8.0 software package (SAS, Cary, NC). Continuous variables presented as median values with ranges were compared using nonparametric tests or Student *t* test if the data were normally distributed; categorical variables, as numbers with percentages were evaluated with Pearson's χ^2 test or Fisher Exact Test. A p value less than .05 was considered to be statistically significant.

RESULTS

The characteristics of the 11 patients switched from standard to prolonged-release tacrolimus are shown in Table 1 Mean age at transplantation was 4.3 years (range, 1.1–8.2). Mean age at conversion was 11.3 years (range, 6.9–16.3). The mean duration of follow-up was 12.0 months (range, 2.4–20.4). Underlying diseases included biliary atresia (n = 9), Wilson's disease (n = 1), and ornithine transcarbamylase deficiency (n = 1). Tacrolimus trough levels are shown in Fig 1. Trough levels just before conversion did not correlate with prolonged-release values at 4 weeks thereafter (P = .21). The average ratios of standard to prolonged-release tacrolimus trough levels at 1, 2, and 4 weeks after conversion are shown in Fig 2. Mean tacrolimus trough levels after conversion decreased gradually. The trough level 4 weeks post conversion was 0.92 of standard tacrolimus, a difference that was not significant (P = .26). The outcomes of conversion are shown in Fig 3. Two patients discontinued prolonged-release tacrolimus owing to abnormal liver function tests and neurological abnormalities, respectively (Fig 4). One patient returned to standard tacrolimus and the other was switched to cyclosporine, with resolution of symptoms soon after discontinuation.

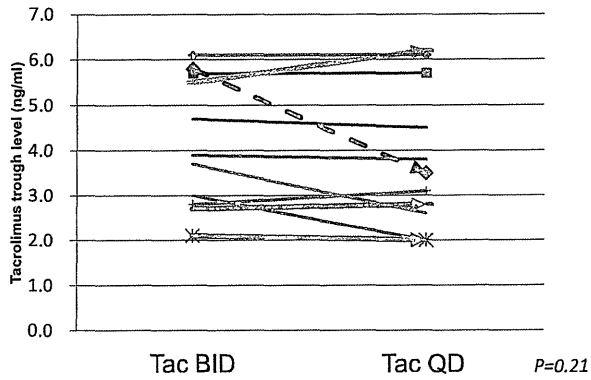

Fig 1. Prolonged-release tacrolimus trough levels 4 weeks after conversion. Each line indicates the change in the tacrolimus trough level for an individual patient. Standard tacrolimus (Tac BID) trough levels were measured just prior to conversion, and prolonged-release tacrolimus (Tac QD) trough levels were measured 4 weeks after conversion (P = .21; paired t test).

Of the 9 children who continued with prolonged-release tacrolimus, 89% of patients were satisfied with once-daily administration and the capsule formulation, although younger patients needed training on how to swallow capsules. In the overall assessment, all patients were satisfied with conversion to prolonged-release tacrolimus.

Table 1. Patient Characteristics

Patient	Gender	Age at Tx	Original Disease	Age at CV	BW (kg)	Observation (mo)	Tac BID Dose (mg)	Other IS
1	Male	4.1	Biliary Atresia	16.3	53	14.3	1.5	PSL
2	Male	1.3	Biliary Atresia	11.4	38	20.4	2.5	PSL
3	Female	1.1	Biliary Atresia	10.3	28	14.3	1.5	MMF
4	Female	8.2	Wilson's disease	15.8	49	14.3	2	None
5	Male	5.9	Biliary Atresia	13.3	45	10.1	3	PSL
6	Female	1.6	Biliary Atresia	8.3	23	3.6	0.5	PSL
7	Female	1.4	Biliary Atresia	7.6	21	2.4	0.8	PSL
8	Female	7.2	Biliary Atresia	13.2	39	2.4	2	PSL
9	Female	6.0	Biliary Atresia	8.8	26	20.0	3	PSL + MMF
10	Male	4.7	Biliary Atresia	7.7	29	18.3	1	PSL
11	Female	5.6	OTCD	6.9	20	3.1	1.2	None

Tx, transplant; CV, conversion; BW, body weight; IS, immunosuppression; PSL, prednisolone; MMF, mycophenolate mofetil; OTCD, ornithine transcarbamylase deficiency.

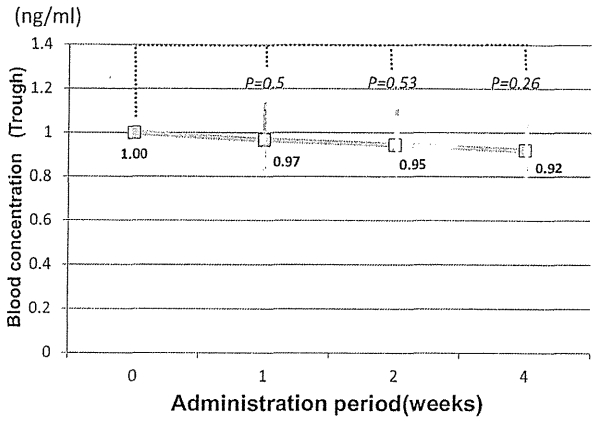

Fig 2. Mean prolonged-release tacrolimus trough levels over time. Tacrolimus trough level ratios were plotted for 1, 2, and 4 weeks postconversion. Week 0: standard tacrolimus trough level = 1. Each number corresponds to (prolonged-release tacrolimus trough level)/(standard tacrolimus trough level). Each *P* value represents a comparison with the standard tacrolimus trough level (week 0).

DISCUSSION

Prograf, an immediate-release formulation, is administered twice daily to prevent and treat allograft rejection in liver transplant patients. A prolonged-release formulation (Graceptor) has been developed to provide once-daily dosing; however, it is only available in capsule form.

Liver transplant patients are generally monitored with routine blood tests that include liver function tests (LFTs). Some patients may no longer require immunosuppression. However, pathological changes are sometimes detected even when blood test results are within the normal range.[1] Therefore, patients require life-long immunosuppression. Once-daily administration is also beneficial for drug compliance in pediatric patients who require continued immunosuppression.

This study was designed to determine the efficacy, safety, and level of patient satisfaction from a switch from the standard tacrolimus to the prolonged-release formulation. Trunečka et al studied the safety and efficacy of dual-therapy regimens of twice-daily tacrolimus and once-daily tacrolimus (Advagraf) administered with steroids among 475 adult primary liver transplant recipients who did not receive antibody induction.[2] The rate of biopsy-proven acute rejection episodes at 24 weeks was 33.7% for standard vs 36.3% for the prolonged-release tacrolimus group. At 12 months, the number of episodes requiring treatment was similar for patients on both standard and prolonged-release forms (28.1% and 24.7%, respectively). Twelve-month patient and graft survivals were 90.8% and 85.6% vs 89.2% and 85.3% for the standard vs prolonged-release tacrolimus groups, respectively. Adverse event profiles were similar. Prolonged-release tacrolimus was well tolerated with similar efficacy and safety profiles as standard tacrolimus. In our study, 2 patients experienced unexpected reactions. Close observation after conversion is required even if patients have had an uneventful course on standard tacrolimus.

Beckebaum et al reported that switching of adult liver transplant recipients from twice-daily to once-daily tacrolimus on a 1:1 mg basis was associated with lower tacrolimus trough levels in nearly two-thirds of patients (>25% lower in 28.8% of patients) at 1 week postconversion. Tacrolimus concentrations were approximately 10% lower than baseline at week 1 without any dose changes, remaining significantly lower at week 2 and prompting us to increase the dosage of tacrolimus with once-daily dosing in the corresponding patients. These observations suggested that close monitoring of tacrolimus trough levels is essential during the early postconversion period. In our study, pediatric liver transplant recipients displayed lower tacrolimus trough levels after conversion, consistent with results among adults.[3]

Satisfaction levels were excellent among both patients and their parents. In general, medication adherence tends to decrease during adolescence. So far only a capsule form is available on the market. Therefore, only patients who can take capsules can benefit from once-

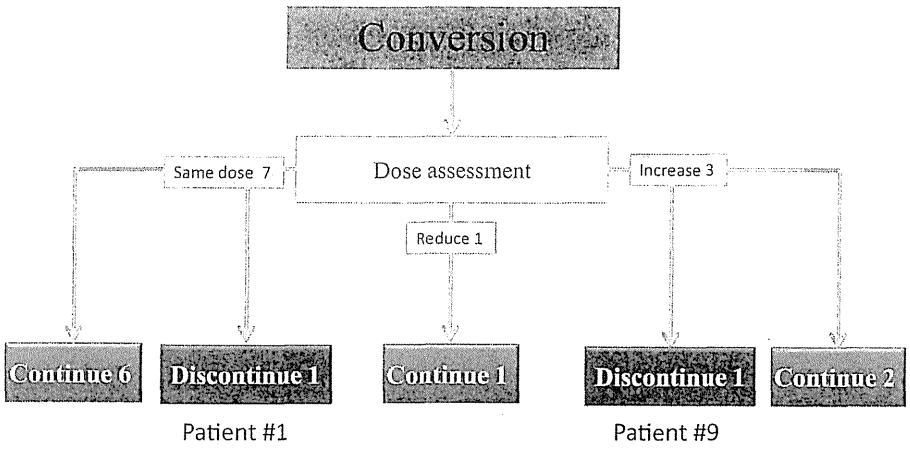

Fig 3. Summary of outcomes after conversion. The flowchart shows patient outcomes after conversion. The numbers at each step represents the number of patients. Patients 1 and 9 discontinued tacrolimus.

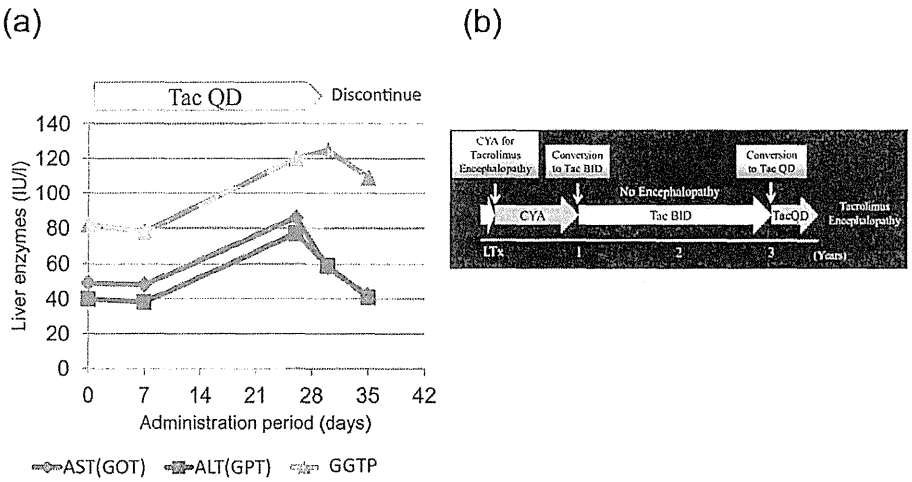

Fig 4. Clinical courses of the patients who discontinued prolonged-release tacrolimus. (a) Patient 1 had abnormal liver function tests after switching to prolonged-release tacrolimus, which normalized after prolonged-release tacrolimus was switched back to standard tacrolimus. (b) In Patient 9, tacrolimus encephalopathy recurred after conversion to prolonged-release tacrolimus, although the patient did not experience neuropathy for more than 2 years on standard tacrolimus. Tac BID: standard tacrolimus; Tac QD: prolonged-release tacrolimus; CyA: cyclosporine; AST: aspartate aminotransferase; ALT: alanine transaminase; GGTP: gammaglutamyl transpeptidase; LTx: liver transplant.

daily dosing. A granule-type formulation is awaited for once-daily tacrolimus, as is available with standard tacrolimus.

In conclusion, prolonged-release tacrolimus was useful for pediatric patients after LRDLT. Trough levels after conversion were compatible with those before conversion. Most patients were satisfied with prolonged-release tacrolimus. However, some patients failed conversion because of unexpected responses. Close observation after conversion is required even if patients have had an uneventful course on standard tacrolimus.

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ELSEVIER

A National Survey of Patients With Intestinal Motility Disorders Who Are Potential Candidates for Intestinal Transplantation in Japan

T. Ueno, M. Wada, K. Hoshino, S. Sakamoto, H. Furukawa, and M. Fukuzawa

ABSTRACT

Intestinal motility disorders are a major cause of intestinal failure. Severe cases such as idiopathic pseudo-obstruction represent life-threatening illnessed. Intestinal transplantation is a treatment for severe motility disorders with irreversible intestinal failure. However, the prevalence of severe motility disorders is unknown. We performed a national survey to identify patients with intestinal motility disorders who require an intestinal transplant. The national survey of 302 institutions treating intestinal motility disorders identified 147 patients treated from 2006 to 2011 at 46 institutions. The mean patient age was 12.1 years (range, 0.3–77.5). The mean age of onset was 3.0 years (range, 0.0–68.8). Diagnoses included chronic idiopathic intestinal pseudo-obstruction (n = 96), Hirschsprung disease (n = 29), megacystis microcolon intestinal hypoperistalsis syndrome (n = 18), and other (n = 6). There were 126 survivors and 21 patients who died during the last 5 years. The mortality rate was 14.3%. Eighty-five percent of patients required parenteral nutrition for more than 6 months, which was defined as irreversible intestinal failure. Among surviving patients with irreversible intestinal failure, 8 (9.4 %) developed hepatic failure with jaundice and 27 (31.8%) 2 or more central vein thromboses. In all, at least 35 patients (41%) with irreversible failure due to intestinal motility disorders may be candidates for transplantation. The prevalence of severe intestinal motility disorders was elucidated in Japan. Severe cases should be referred to transplant centers.

INTESTINAL MOTILITY DISORDERS are a major cause of intestinal failure. Severe cases such as idiopathic pseudo-obstruction are life-threatening. Causes of intestinal motility disorders seem to be multifactorial, and only a few have been elucidated. The prognosis is poor for patients with severe illness. The outcome for intestinal failure has improved dramatically due to the development of parenteral nutrition (PN). However PN-related complications, such as central venous catheter infection, thrombosis of venous access points, and PN-associated cholestasis of the liver, are still major problems for patients with intestinal failure. Intestinal transplantation is a treatment for irreversible intestinal failure due to severe disorders of intestinal motility that can significantly improve the prognosis and quality of life for patients. Progress in intestinal transplantation has improved survival. However, the prevalence of severe intestinal motility disorder is unknown. The Therapeutic Guidelines for Intestinal Failure Study Group performed a national survey to identify patients with intestinal motility disorders requiring an intestinal transplant.

METHODS

This national survey was designed as a 5-year retrospective observation study involving 302 institutions that treat intestinal motility disorders. These institutions were members of the Japanese Society of Pediatric Surgeons, the Japanese Society for Small Bowel Transplantation, and the Japanese Study Group for Home Parenteral and Enteral Nutrition. After an initial survey, a questionnaire about each patient was sent to responding institutions from the data center based at Osaka University. Patients with intestinal

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failure treated at each institution from 2006 to 2011 were included. Exclusion criteria were: (1) final diagnosis other than intestinal failure, (2) intestinal failure ultimately resolved, (3) intestinal failure resulting from malignancy, and (4) intestinal failure secondary to diseases in other organs. There were 354 patients reported by 69 institutions. Irreversible intestinal failure was defined as dependence on PN for more than 6 months. Out of these 354 patients, patients with intestinal failure due to motility disorders were identified. The following factors were assessed for possible associations with indications for intestinal transplantation: diagnosis, patient age, age of onset, sex, patient outcome, PN status, liver function tests (LFTs), and central line access. This study was approved by the Osaka University Hospital institutional review board and was supported by Health Science Research Grants from the Ministry of Health, Labor and Welfare of Japan.

RESULTS

There were 147 patients with intestinal motility disorders identified from 46 institutions. The prevalence was approximately one in one million. There were 55 male and 92 female patients. The female-to-male ratio was about 2:1. The mean patient age was 12.1 years (range, 0.3–77.5 years). The mean age of onset was 3.0 years (range, 0.0–68.8 years). Causes of intestinal failure are shown in Fig 1. During the observation period, 126 patients survived and 21 patients died. The mortality rate was 14.3%.

Detailed analysis was added for survivors to determine indications for intestinal transplantation. Of the surviving patients, 91 (62.0%) needed PN at least once a week, and 85 (57.8%) required PN for more than 6 months. Those 85 patients were defined as having irreversible intestinal failure. The following analyses were carried out for patients with irreversible intestinal failure. Catheter-related complications were assessed. The site of central vascular access (internal jugular vein, subclavian vein, and femoral vein) was reported. The number of venous access failures is shown in Fig 2. Twenty-seven patients (31.9%) had 2 or more instances of central vascular access loss.

There were 61 patients (71.8%) who developed abnormal LFTs suggestive of liver injury from PN, including 8 patients (13%) with jaundice. They were considered to have severe liver injury resulting from PN.

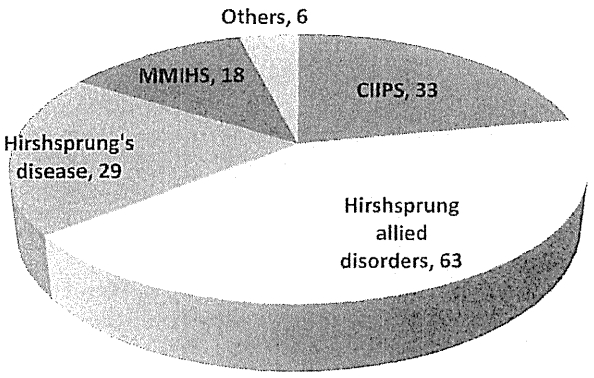

Fig 1. Causes of intestinal failure (n = 147). CIIPS, chronic idiopathic intestinal pseudo-obstruction; MMIHS: megacystis microcolon intestinal hypoperistalsis syndrome.

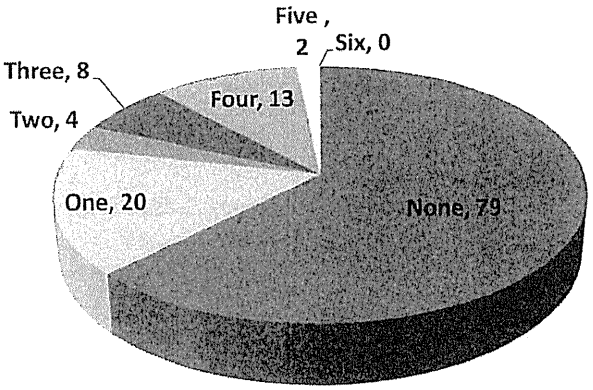

Fig 2. Number of central vascular access losses (n = 126). The number on the left indicates the number of vascular access losses.

Fifty-eight patients required at least 1 hospitalization in the previous year. Nineteen patients (22.4%) required hospitalization for more than 6 months over the previous year. Their quality of life was severely impaired.

A flowchart for identifying possible candidates for intestinal transplantation is shown in Fig 3. Patients dependent on PN for more than 6 months were defined as having irreversible intestinal failure. Those with more than 2 central vascular access losses, and abnormal LFTs with jaundice were considered for candidates for intestinal transplantation. Patients who died from liver failure or infection might be saved by intestinal transplant. They might be candidates for intestinal transplant too. In total, 45 patients were potential candidates for intestinal transplantation. Additionally, the 19 patients who were hospitalized for more than 6 months can be potential candidates given their poor quality of life.

DISCUSSION

Intestinal motility disorders include a wide range of diseases. Chronic intestinal pseudo-obstruction, the most common type of intestinal mobility disorder, is caused by ineffective intestinal contraction. It is characterized by symptoms and signs of intestinal obstruction.[1] Intestinal transplantation can significantly improve the prognosis and quality of life of patients with intestinal motility disorders in Japan.[1] Survival rates in Japan are comparable with rates from the international intestinal transplant registry.[2]

Previously, the prevalence of intestinal motility disorders in Japan was unknown. It was estimated that there were 100 severe cases nationwide. This study supports this figure because surveillance was of a large enough scale to cover the entire nation.

There were over 40 patients who may need intestinal transplantation. However, only 3–4 a year intestinal transplants are performed in Japan, even if 10 times as many patients may be cured by intestinal transplantation.

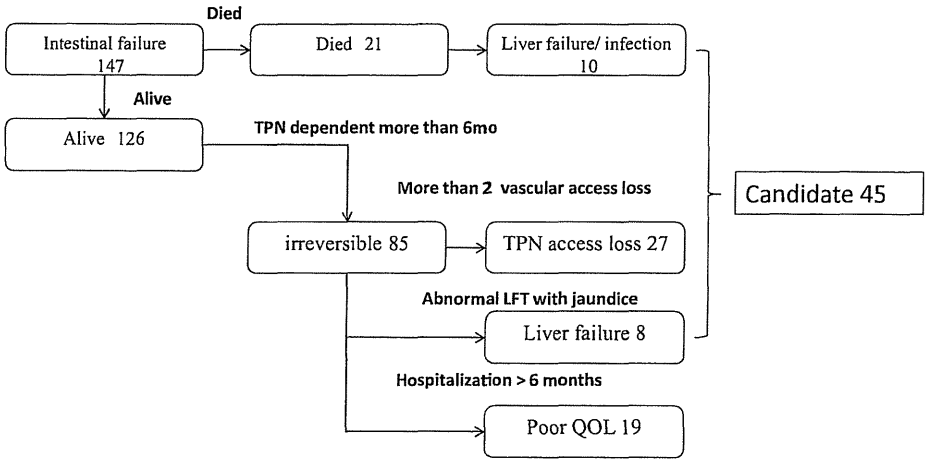

Fig 3. Candidates for intestinal transplantation. TPN, total parental nutrition; QoL, quality of life.

There were 2 major reasons for the relative paucity of intestinal transplants in Japan. One reason is the lack of available organs. For a long time, very few organs from deceased donors were obtainable in Japan. As with other solid organs, most intestinal transplants in Japan are performed with living donors. The shortage of organs has been alleviated due to a new act on organ transplantation that went into effect in 2010. However, the number of intestinal transplant has remained steady.

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

Some patients develop liver failure with intestinal motility disorders. These patients need simultaneous liver-intestine 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. Current organ allocation guidelines do not allow for simultaneous combined liver-intestine organ retrieval; thus, a simultaneous liver-intestine transplant is impossible from deceased donor sources.

Previously, the laws on organ transplantation banned donors below 15 years of age. Intestinal transplants were not previously possible in infants because of organ size mismatch. Such patients will benefit from intestinal transplants in the future. Moreover, younger patients sometimes develop liver failure.[3] Multiorgan transplantation is a good option for such patients.[4]

It is difficult to determine the optimal timing for intestinal transplants to treat intestinal failure associated with intestinal motility disorders. Severe cases of intestinal motility disorders should be referred to institutions with expertise in transplantation.

In conclusion, the prevalence of severe motility disorders in Japan was elucidated. Patients with irreversible intestinal failure from intestinal motility disorders may be candidates for intestinal transplantation. Severe cases of motility disorder should be referred to transplant centers. Further investigation for patient details is required.

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ORIGINAL ARTICLE

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

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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.

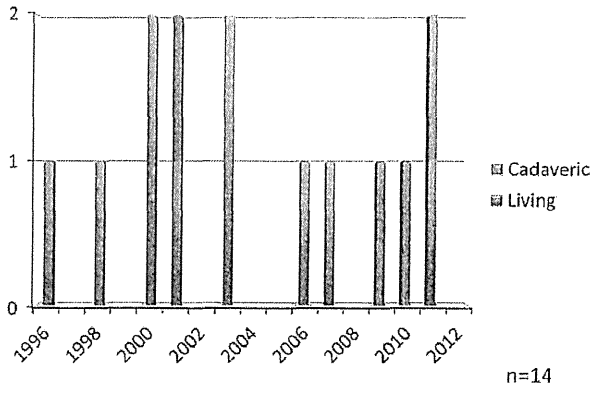

Fig. 1 Number of intestinal transplants by year