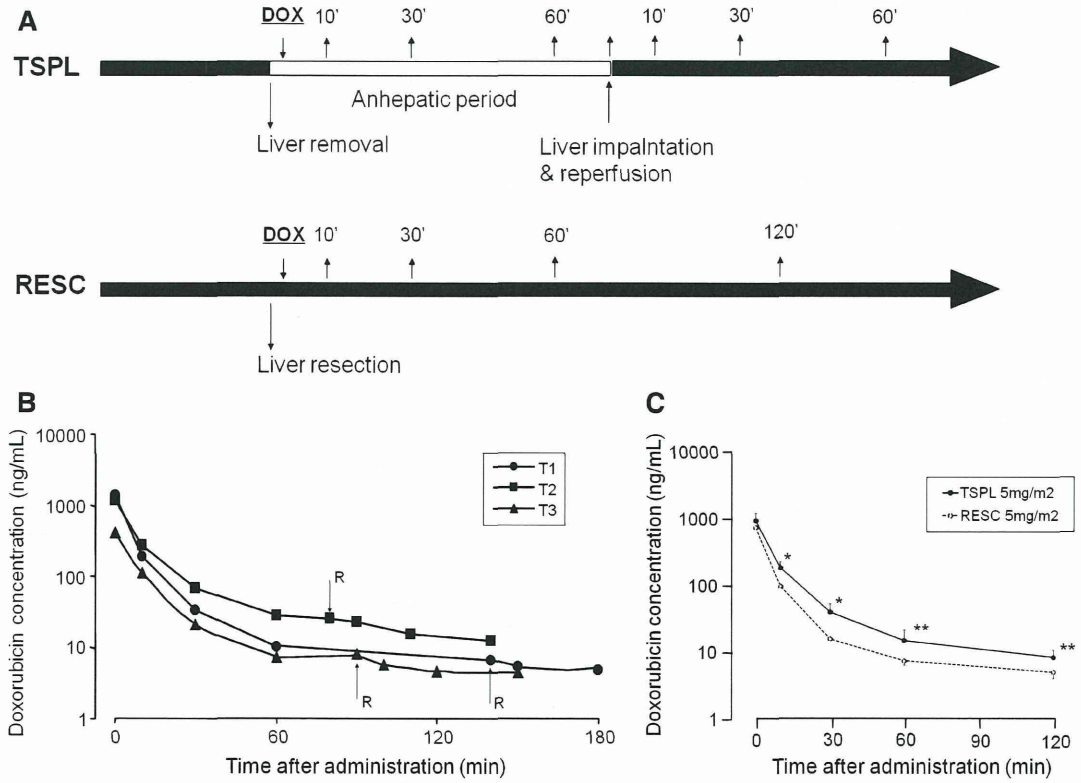

Fig. 1 Perioperative administration of doxorubicin in patients undergoing liver transplant or resection. **a** A schematic depicting doxorubicin (DOX) administration and sample collection. DOX was administered 5 min after the removal of the cirrhotic liver (TSPL) or liver resection with portal vein tumor thrombi (RESC). Peripheral blood samples were obtained at 0, 10, 30, 60, 120, and 180 min, as indicated. Blood samples were also obtained at the same intervals after reperfusion in the TSPL group. **b** Change in serum doxorubicin concentration in TSPL patients after DOX administration (5 mg/m^2). Each line indicates the serum DOX concentration in an individual TSPL patient (T1, T2, and T3). R, reperfusion. **c** The mean change in serum DOX concentration in the TSPL ($n = 3$) and RESC ($n = 5$) groups after DOX administration (5 mg/m^2). Data are expressed as mean ± standard error. $*p < 0.05$, $**p < 0.1$

group; however, only albumin and Child-Pugh classification were worse among TSPL patients. Renal function (serum creatinine level) did not differ between the groups ($p = 0.3118$).

The mean duration of the anhepatic period (from clamp of the portal vein of the recipient to reperfusion) was 101 min in the TSPL group. We compared serum DOX concentrations at 0, 10, 30, and 60 min after DOX administration; data at 120 min served as a reference. Reperfusion seemed to have almost no influence on the serum DOX concentration (Fig. 1b). The concentration from 0 min to 120 min (C0–C120) is depicted in Table 2 and Fig. 1c. At 10 and 30 min after DOX administration, serum DOX concentrations were significantly higher in TSPL patients than in RESC patients. Although the levels at 60 and 120 min were numerically higher in the TSPL group, the data only trended toward statistical significance. The other pharmacokinetic parameters are also described in Table 2. The area under curve from 0 to 120 min (AUC_{120}) was numerically higher in TSPL patients and approximately 1.5-fold higher than in RESC patients.

We employed both the one-compartment and two-compartment models to evaluate half-life ($T_{1/2}$) because the $T_{1/2}$ of alpha phase (also known as the distribution phase) was longer during the anhepatic period and the $T_{1/2}$ of beta phase (also known as the elimination phase) was unchanged in dogs [25, 26]. These findings indicated that the pharmacokinetic analysis of DOX during the anhepatic period is more important during the alpha phase, and for this reason, we decided to employ the one-compartment model. In our hands, the two-compartment model revealed that the $T_{1/2}$ of alpha phase was longer in the TSPL group than in the RESC group, although the difference did not reach statistical significance, and the $T_{1/2}$ of beta was shorter among TSPL patients than RESC patients. In contrast, the one-compartment model indicated that the $T_{1/2}$ trended longer in the TSPL group than in the RESC group.

Table 1 Characteristics of liver transplant (TSPL) and resection (RESC) patients who were treated with 5 mg/m^2 doxorubicin

Variables	TSPL	RESC	*p* value
v*n*	3	5	
Age	57 ± 5.4	56 ± 2.0	0.6939
Sex	2 (67 %)	4 (80 %)	0.6733
Male (%)			
Body high (cm)	164 ± 4.1	171 ± 2.7	0.2213
Body weight (kg)	66 ± 5.2	70 ± 2.8	0.5739
Body surface area (m^2)	1.67 ± 0.07	1.77 ± 0.04	0.3129
Hepatitis			
HBV (%)	1 (33 %)	3 (60 %)	0.4652
HCV (%)	2 (67 %)	1 (20 %)	0.1869
Preoperative liver function			
Aspartate aminotransferase (IU/L)	82 ± 30	53 ± 14	0.4460
Alanine aminotransferase (IU/L)	69 ± 31	46 ± 11	0.5300
Prothrombin time-INR	1.33 ± 0.15	1.22 ± 0.02	0.5299
Total bilirubin (mg/dL)	4.8 ± 1.31	0.9 ± 0.16	0.0918
Albumin (g/dL)	2.7 ± 0.20	3.9 ± 0.13	**0.0079**
Creatinine (mg/dL)	0.6 ± 0.10	0.8 ± 0.10	0.3118
Child-pugh score	10.7 ± 1.5	5.0 ± 0.0	0.0599
Child-pugh classification			
A	0	5 (100 %)	**0.0183**
B	1 (33 %)	0	
C	2 (67 %)	0	
MELD score	15.0 ± 2.5	8.2 ± 0.37	0.1109
Anhepatic period (min)	101 ± 22	N/A	
Cold ischemia time (min)	69 ± 18	N/A	
Warm ischemia time (min)	46 ± 12	N/A	
Operation period (min)	703 ± 41	541 ± 95	0.1767
Estimated blood loss (min)	4,307 ± 1,699	3,984 ± 2,226	0.9120
Graft or remnant liver lobe			
Left (%)	1 (33 %)	3 (60 %)	0.4652
Right (%)	2 (67 %)	2 (40 %)	
GW/SLV	0.54 ± 0.06	N/A	
Dose of doxorubicin (mg/m^2)	5	5	

Bold values indicate statistical significance at $p < 0.05$

MELD score, model for end stage liver disease score; RESC, patients who underwent liver resection and portal vein tumor thrombi removal due to hepatocellular carcinoma; TSPL, patients who underwent liver transplantation due to liver cirrhosis and hepatocellular carcinoma; and *GW/SLV,* graft weight/standard liver volume

Change in serum DOX concentration in TSPL patients at 3, 5, 10, and 15 mg/m^2 DOX

We summarized TSPL patients' characteristics in Table 3. Ninety percent of the patient population was male, and the mean body surface area was 1.78 m^2. The mean

Table 2 Pharmacokinetic parameters in liver transplant (TSPL) and resection (RESC) patients after administration of 5 mg/m2 doxorubicin

	TSPL	RESC	*p* value
n	3	5	
Dose of doxorubicin (mg/m^2)	5	5	
Plasma concentration (ng/mL)			
C0	975 ± 165	760 ± 171	0.2575
C10	189 ± 46	99 ± 12	**0.0233**
C30	40 ± 13.8	16 ± 2.9	**0.0315**
C60	15 ± 6.6	7.4 ± 1.1	0.0903
C120	8.3 ± 2.4	5.0 ± 1.0	0.0940
AUC_{120} (ng min/mL)	9,642 ± 2,519	6,162 ± 877	0.0808
One-compartment model			
A	974 ± 173	760 ± 171	0.2583
α	0.156 ± 0.20	0.197 ± 0.019	0.1056
$T_{1/2}$(min)	4.6 ± 0.54	3.6 ± 0.32	0.0774
Two-compartment model			
A	902 ± 267	739 ± 173	0.3040
B	73 ± 27	22 ± 5	**0.0235**
α	0.183 ± 0.020	0.218 ± 0.018	0.1301
β	0.023 ± 0.004	0.014 ± 0.002	**0.0359**
$T_{1/2}$ α(min)	3.9 ± 0.5	3.3 ± 0.3	0.1276
$T_{1/2}$ β(min)	31.7 ± 4.9	55.4 ± 10.9	0.0822

Bold values indicate statistical significance at $p < 0.05$

AUC_{120}, area under concentration curve from 0 to 120 min; RESC, patients who underwent liver resection and portal vein tumor thrombi removal due to hepatocellular carcinoma; and TSPL, patients who underwent liver transplantation due to liver cirrhosis and hepatocellular carcinoma

MELD score was 16.0. Because one patient was received a transplanted liver from a deceased donor, the mean cold ischemia time was 137 min and one graft liver was whole liver. However, the anhepatic period was 118 ± 11 min, and there appeared to be no large difference among the patients. We observed changes in serum DOX concentration at 3, 5, 10, and 15 mg/m^2 (Fig. 2). Pharmacokinetic parameters are summarized in Table 4. AUC_{120} increased in a dose-dependent manner, with the exception that AUC_{120} at 10 mg/m^2 was slightly lower. The $T_{1/2}$ of serum DOX concentrations was prolonged in alpha phase of the one-compartment model and in beta phase of the two-compartment model, according to dose escalation of DOX. Maximum serum concentration was 2,440 ng/mL at 15 mg/m^2 DOX administration.

Adverse events in TSPL patients at 5, 10, and 15 mg/m^2 DOX

We evaluated adverse events in TSPL patients using CTCAE version 4.0 during the first 7 days after liver

Table 3 Characteristics of transplant (TSPL) patients

Variables	TSPL
n	12
Age	53 ± 7.1
Sex	
Male (%)	11 (92 %)
Body high (cm)	168 ± 1.7
Body weight (kg)	71 ± 3.4
Body surface area (m^2)	1.78 ± 0.05
Hepatitis	
HBV (%)	3 (25 %)
HCV (%)	7 (58 %)
Preoperative liver function	
Aspartate aminotransferase (IU/L)	58 ± 11
Alanine aminotransferase (IU/L)	47 ± 12
Prothrombin time-INR	1.68 ± 0.18
Total bilirubin (mg/dL)	5.5 ± 1.51
Albumin (g/dL)	2.9 ± 0.15
Creatinine (mg/dL)	0.8 ± 0.11
Child-pugh score	5.0 ± 0.0
Child-pugh classification	
B	4 (33 %)
C	8 (67 %)
MELD score	16.0 ± 1.43
Anhepatic period (min)	118 ± 11
Cold ischemia time (min)	137 ± 46
Warm ischemia time (min)	44 ± 4
Operation period (min)	811 ± 36
Estimated blood loss (min)	7,975 ± 1,769
Graft liver lobe	
Left (%)	2 (17 %)
Right (%)	9 (75 %)
Whole (%)	1 (8 %)
GW/SLV	0.54 ± 0.06
Dose of doxorubicin (mg/m^2)	3–15

GW/SLV, graft weight/standard liver volume; MELD score, model for end stage liver disease score; and TSPL, patients who underwent liver transplantation due to liver cirrhosis and hepatocellular carcinoma

transplantation (Table 5). Because of liver transplantation, Grade 3–4 decreased platelet count and hyperbilirubinemia was noted in almost all patients. Grade 1 diarrhea at 5 mg/m^2 was noted owing to elementary diet. Two patients at 10 mg/m^2 presented with Grade 1 abnormal echocardiogram (sinus tachycardia). Other Grade 1–2 adverse events were compatible with the regular postoperative course after liver transplantation. Regarding DOX-related adverse drug reactions, both symptoms and laboratory data were unremarkable.

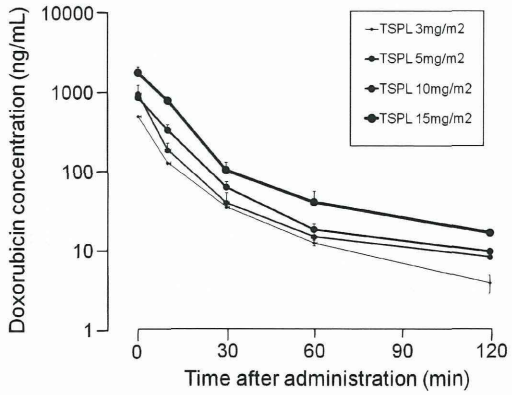

Fig. 2 The mean change in serum doxorubicin concentration in liver transplant patients (TSPL) treated perioperatively with 3, 5, 10, or 15 mg/m^2 doxorubicin. Each patient was treated with the indicated dose of doxorubicin ($n = 3$ per dose level). Data are expressed as mean ± standard error

Tumor factors and survival in TSPL patients

As preliminary data, we investigated the recurrence-free survival and overall survival in TSPL patients. Tumor characteristics are summarized in Table 6. Briefly, this patient population featured 58 % multiple HCCs, 50 % exceeding Milan criteria, and no portal vein tumor thrombus. One patient underwent intra-portal 5-fluorouracil infusion. With a median observation period of 4.1 years (range, 1.7–9.9 years), the 5-year recurrence-free survival was 68.8 %, and the overall survival was 100.0 %. Two patients with HCC exceeding Milan criteria experienced HCC recurrence: One patient, who suffered from over 20 HCCs (maximum diameter, 3.3 cm) with microscopic vascular invasion and was treated with 3 mg/m^2 DOX, experienced liver metastasis at 1.0 year post-transplantation. Another patient, who suffered from 4 HCCs (maximum diameter, 1.5 cm) and was treated with 5 mg/m^2 DOX, experienced lymph node metastasis at 5.0 years post-transplantation. The former patient who was treated with 3 mg/m^2 DOX died of HCC at 6.2 years post-transplantation.

Discussion

In the current study, we demonstrated the elevation of serum DOX concentration during the anhepatic period. Briefly, the concentrations at 10 and 30 min after DOX administration (C10 and C30) were elevated two- to three-fold during liver transplantation in comparison with liver resection. $T_{1/2}$ in the one-compartment model tended to be prolonged. In contrast, in the two-compartment model, $T_{1/2}$ α was prolonged, but was not significantly so, and $T_{1/2}$ β

Table 4 Pharmacokinetic data from transplant (TSPL) patients for each dose of doxorubicin

Dose of doxorubicin (mg/m^2)	AUC $_{120}$ (ng min/mL)	One-compartment model			Two-compartment model					
		A	α	$T_{1/2}$ (min)	A	B	α	β	$T_{1/2}\,\alpha$ (min)	$T_{1/2}\,\beta$ (min)
3	6,060	507	0.134	5.52	419	90	0.182	0.0285	3.8	26.6
5	9,642	974	0.156	4.57	902	73	0.183	0.0230	3.9	31.7
10	12,227	880	0.094	7.58	880	25	0.104	0.0083	6.6	83.1
15	25,882	1,804	0.084	8.87	3,038	38	0.139	0.0069	5.0	100.0

AUC_{120}, area under concentration curve from 0 to 120 min; TSPL, patients who underwent liver transplantation due to liver cirrhosis and hepatocellular carcinoma

Table 5 Adverse events during the first 7 days after liver transplantation

Dose of doxorubicin (mg/m^2)	5		10		15	
CTCAE Grade	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Symptom						
Diarrhea	1	0	0	0	0	0
Rash	0	0	0	0	0	0
Fever	0	0	0	0	0	0
Biliary tract infection	0	0	0	0	0	0
Other infection	0	0	0	0	0	0
Laboratory data						
Abnormal ECG	0	0	2	0	0	0
Neutropenia	1	0	2	0	1	0
Anemia	3	0	3	0	3	0
Platelet	0	3	0	3	0	3
Creatinine	0	0	2	0	1	0
Aspartate aminotransferase	3	0	3	0	3	0
Alanine aminotransferase	3	0	3	0	3	0
Alkaline phosphatase	0	0	1	0	0	0
Total bilirubin	0	3	0	3	2	1
Prothrombin time	2	0	1	0	0	0
Albumin	1	0	2	1	3	0

CTCAE Common Terminology Criteria for Adverse Events, version 4.0

tended toward being shortened. The AUC was elevated in a dose-dependent manner. No obvious adverse drug reactions were noted at the maximum dose of DOX during the anhepatic period.

Serum concentrations of drugs, including DOX, have rarely been investigated in liver dysfunction during the anhepatic period. The change in serum DOX concentration during the anhepatic period was marked by rapid decline after administration and two- to threefold elevation at C10 and C30. First, the rapid decrease after DOX administration was also noted in the normal liver [21]. This rapid decrease might be a result of distribution to the other organs and blood vessels [30] (e.g., DOX is mainly distributed to the spleen and lung in rats). At C10 and C30, serum DOX concentrations were sustained at two- to threefold; these data are similar to previous studies in dogs, which compared concentrations during the anhepatic period versus in normal whole liver [25, 26]. Using both one- and two-compartment models, we observed that DOX $T_{1/2}$ was prolonged by minutes. In contrast, $T_{1/2}$ β was shortened in the two-compartment model by approximately 10 min. These findings are compatible with previous reports of serum concentration in dogs [25].

An additional discussion point is the effect of the duration of the anhepatic period. The anhepatic period is regularly within 2 h (especially in living donor liver transplantations), and our findings demonstrate that the length of the anhepatic period appears to have limited influence on the serum DOX concentration. In comparisons of normal and cirrhotic liver, the DOX concentration in cirrhotic liver reached levels that were six- to eightfold higher than in normal liver at 48 h after DOX administration [31, 32]. In contrast, serum DOX concentration during the anhepatic period was limited two- to threefold higher

Table 6 Tumor factors in liver transplant (TSPL) patients

Variables	TSPL
n	12
HCC	
Multiple (%)	7 (58 %)
Maximum size (cm)	1.3 ± 0.3
PVTT (%)	0
Exceeding Milan criteria(%)	6 (50 %)
Preoperative treatment	
Transcatheter arterial chemo-embolization (%)	5 (42 %)
Local ablation (radiofrequency, microwave) (%)	5 (42 %)
Complete necrosis (%)	2 (17 %)
AFP (ng/mL)	527 ± 313
Histology	
Early HCC	1 (8 %)
Well differentiated HCC	2 (17 %)
Moderately differentiated HCC	4 (33 %)
Poorly differentiated HCC	3 (25 %)
Micro PVTT (%)	1 (8 %)

AFP, α-fetoprotein; *HCC,* hepatocellular carcinoma; *PVTT,* portal vein tumor thrombi; and *TSPL,* patients who underwent liver transplantation due to liver cirrhosis and hepatocellular carcinoma

in patients undergoing transplant than in those undergoing resection. In other words, the factor of liver function (anhepatic or not) appears to influence serum DOX concentration only between 30 min and 120 min after DOX administration. The elevation of the serum DOX concentration is likely limited because the anhepatic period is so short.

The final discussion points regarding pharmacokinetic analysis are the AUC and peak serum DOX concentrations during the anhepatic period. As the administered dose of DOX escalated, the AUC increased to 25,000 ng min/mL (approximately 400 ng h/mL), the peak DOX level reached 2,500 ng/mL in actual measurements and 3,000 ng/mL in estimates calculated from the one- and two-compartment models. The peak serum DOX concentration reportedly contributes to cardiac toxicity in addition to cumulative dose [33–35]. From our findings during the anhepatic period, the AUC of 15 mg/m^2 (our maximum dose) was much lower than when DOX was administered as a systemic bolus; however, the peak level of 15 mg/m^2 was almost equal to a systemic bolus administration of 150 mg/m^2 DOX in previous studies [36, 37]. When comparing the adverse events between "reported 150 mg/m2 of bolus DOX administration" and "our 15 mg/m2 of DOX during anhepatic period," the reported data showed 50 % of febrile neutropenia and 16.7 % of Grade 3–4 nausea/vomiting [36], our data showed 100 % of Grade 3/4 thrombocytopenia, 33 % of hyper bilirubinemia, and no cardiac toxicities, and our data were compatible with "the regular postoperative course" after living donor liver transplantation. The adverse events differed markedly between the previous reports and our data in the present study and may be associated with different causes (adverse drug reaction in the previous report versus regular postoperative course in the present report). Therefore, these might be non-drug-related adverse events that depend on conditions other than peak DOX level, which would indicate that our series did not reveal any severe adverse drug reactions. There remains the possibility that the differences were caused by AUC. However, there is a persistent possibility of severe adverse drug reactions in future series. It will be necessary to check patients' vital signs, physical status, and examinations carefully during any phase II study, because of high peak serum DOX concentration during the anhepatic period.

Regarding the anticancer effect of DOX, we achieved approximately 70 % 5-year recurrence-free survival and 100 % 5-year overall survival in this series. However, a previous randomized trial revealed that adjuvant chemotherapy is ineffective after transplantation [19]. They administered 15 mg/m^2 of DOX intra-operatively (they did not describe whether or not this was during the anhepatic period). Our maximum dose was 15 mg/m^2 DOX during the anhepatic period; the serum DOX concentration did reach 10–100 ng/mL until 120 min. Our previous evaluation showed that the IC_{50} of DOX in several cultured hepatocellular carcinoma cell lines varied from 10 to 100 ng/mL [30]. Although it is difficult to keep serum DOX concentration similar to in vitro studies, the serum concentration appeared to exceed the IC_{50}s demonstrated in vitro.

The recommended dose for DOX during the anhepatic period should be 15 mg/m^2, with careful monitoring for adverse drug reactions. Additional studies, such as a phase II study, are needed to verify adverse drug reactions and should be paired with monitoring of changes in mAFP-expressing cells during the perioperative period to evaluate efficacy. Several researchers have mentioned the existence of HCC cells and/or a niche in the bone marrow in published work [38–40], and it is necessary to evaluate bone marrow cells during the perioperative period. The main limitation of this study is the difficulty of distinguishing between adverse drug reactions and regular postoperative course, and higher doses of DOX might be necessary.

In conclusion, up to 15 mg/m^2 DOX was safely administered during the anhepatic period. However, further investigation is necessary to estimate treatment efficacy, with careful monitoring of adverse events.

Conflict of interest The authors declare no conflicts of interest.

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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.

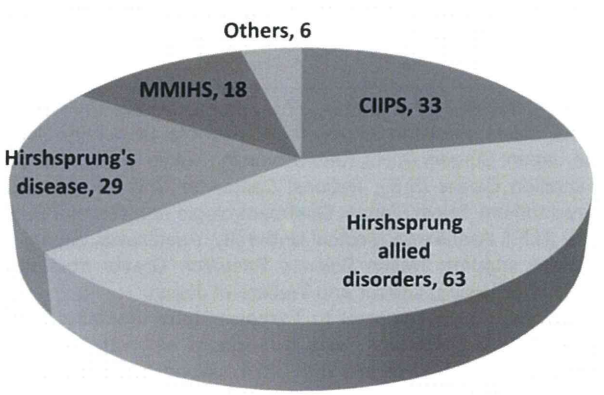

Fig 1. Causes of intestinal failure (n = 147). CIIPS, chronic idiopathic intestinal pseudo-obstruction; MMIHS: megacystis microcolon intestinal hypoperistalsis syndrome.

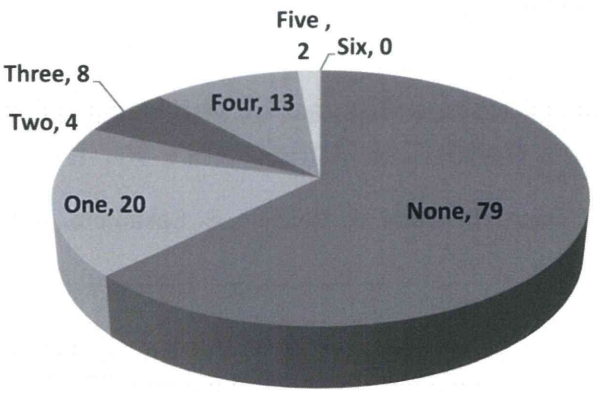

Fig 2. Number of central vascular access losses (n = 126). The number on the left indicates the number of vascular access losses.

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.

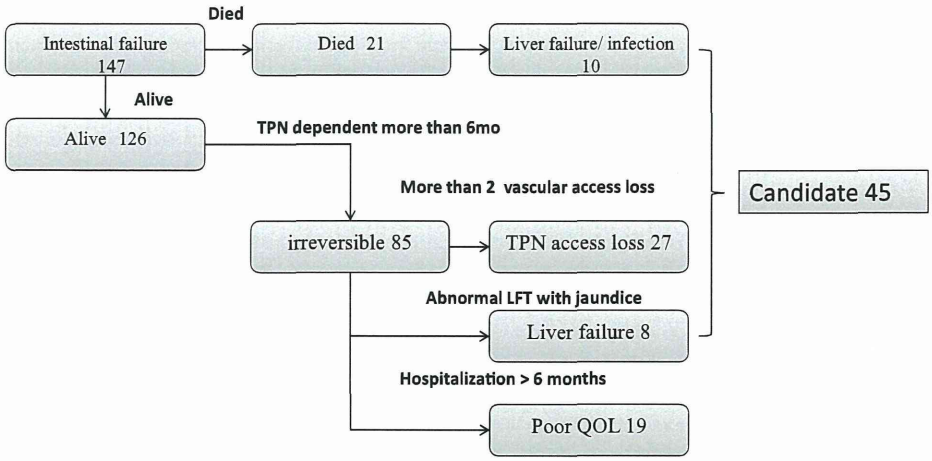

Fig 3. Candidates for intestinal transplantation. TPN, total parental nutrition; QoL, quality of life.

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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