

Title	Multicentre, randomised, placebocontrolled trial of extract of Japanese herbal medicine Daikenchuto to prevent bowel dysfunction after adult liver transplantation (DKB 14 Study)
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BMJ Open Multicentre, randomised, placebo-controlled trial of extract of Japanese herbal medicine Daikenchuto to prevent bowel dysfunction after adult liver transplantation (DKB 14 Study)

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ABSTRACT

Introduction: This multicentre randomised controlled clinical trial will aim to determine the ability of an extract (TJ-100) of Daikenchuto (traditional Japanese herbal medicine; Kampo) to prevent bowel dysfunction in at least 110 patients after liver transplantation (LT).

Methods and analysis: The following co-primary end points will be evaluated on postoperative day 7: total oral and enteral caloric intake, abdominal distension and abdominal pain. The secondary end points will comprise sequential changes of total oral and enteral caloric intake after LT, sequential changes in numeric rating scales for abdominal distension and pain, elapsed time to the first postoperative passage of stool, quality of life assessment using the Gastrointestinal Symptom Rating Scale score (Japanese version), postoperative liver function, liver regeneration rate, incidence of bacteraemia and bacterial strain, trough level of immunosuppressants, occurrence of acute cellular rejection, discharge or not within 2 months after LT, sequential changes of portal venous flow to the graft and ascites discharge. The two arms of the study will comprise 55 patients per arm.

Ethics and dissemination: The study has been conducted according to the CONSORT statement. All participants signed a written consent form, and the study has been approved by the institutional review board of each participating institute and conducted in accordance with the Declaration of Helsinki of 1996. The findings will be disseminated through scientific and professional conferences, and in peer-reviewed journals.

Trial registration number: The DKB 14 Study was registered in the University Hospital Medical Information Network Clinical Trial Registration (UMIN-CTR), Japan (registration number: UMIN000014326) during 2014.

INTRODUCTION

Liver transplantation (LT) is one of the most extensive surgeries for patients with end-

stage liver diseases including liver cirrhosis, hepatocellular carcinoma and acute liver failure. Moreover, protein-energy malnutrition is common in patients with end-stage liver disease requiring LT and closely associated with post-transplant risk of morbidity and mortality.^{1–3} Such patients are usually accompanied by bowel dysfunction after LT due to long surgical durations and wide abdominal incisions, which prevents early postoperative food intake either orally or via an enteral tube and subsequently leads to worsening malnutrition.

The enhanced recovery after surgery (ERAS) protocol has recently been introduced to various types of surgery including organ transplantation.^{4–7} Postoperative management recommended by the ERAS protocol includes the early initiation of normal food intake or enteral feeding after gastrointestinal surgery. Moreover, early tube feeding (within 24 h) is indicated for patients in whom early oral nutrition cannot be initiated due to obvious undernutrition at the time of surgery. However, normal food intake or enteral feeding cannot be started when a patient has bowel dysfunction.

Daikenchuto is a traditional Japanese herbal medicine (Kampo) that has been frequently prescribed to prevent and treat postoperative ileus in Japan.^{8–9} The powdered extract of Daikenchuto, TJ-100 (Tsumura & Co, Tokyo, Japan), is available as an aqueous extract containing 2.2% Japanese pepper, 5.6% processed ginger, 3.3% ginseng and 88.9% powdered maltose syrup. A recent multicentre phase III trial (JFMC40-1001) found that TJ-100 significantly reduced the elapsed time to the first bowel movement compared with a placebo after hepatic

resection.¹⁰ However, the ability of TJ-100 to normalise bowel paralysis after LT and its effects on early total caloric intake delivered orally or enterally after surgery (a key element of the ERAS protocol) have not been prospectively investigated. Therefore, we designed a multicentre, randomised, double-blind, placebo-controlled trial to determine the enhancement effects of TJ-100 on oral and enteral caloric intake and its ability to prevent postoperative paralytic ileus in patients after undergoing living donor LT (LDLT) or deceased donor LT (DDLT).

METHODS AND ANALYSIS

Objective

Postoperative early oral or enteral intake is a crucial element of the ERAS protocol. The DKB 14 Study is a multicentre randomised, double-blind, placebo-controlled trial that aims to determine the enhancement effect of TJ-100 on oral and enteral caloric intake and its ability to prevent postoperative paralytic ileus in patients after LDLT and DDLT.

Resources

A research grant from Tsumura & Co, Tokyo, Japan.

End points

The following primary end points will be evaluated at postoperative day (POD) 7:

- ▶ Total oral or enteral caloric intake;
- ▶ Abdominal distension determined using numeric rating scales (NRS);
- ▶ Abdominal pain determined using NRS.

The following secondary end points will be evaluated:

- ▶ Chronological changes in total oral or enteral caloric intake at POD 3, 5, 7, 10 and 14;
- ▶ Chronological changes in NRS at POD 5, 7, 10 and 14;
- ▶ Elapsed time from extubation until the first postoperative defaecation;
- ▶ Quality of life assessment using the Gastrointestinal Symptom Rating Scale score (Japanese V.1.2) at POD 7 and 14;
- ▶ Liver function determined by measuring total protein, albumin, total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase, choline esterase at POD 3, 5, 7, 10 and 14;
- ▶ Liver regeneration rates determined by CT and calculated as postoperative liver volume/graft liver weight at the time of LT between POD 14 and 21 and graft volume for all patients except those who underwent whole LT;
- ▶ The incidence of bacteraemia until POD 14 and bacterial strain;
- ▶ Trough levels of immunosuppressants at POD 3, 5, 7, 10 and 14;
- ▶ The incidence of acute cellular rejection until POD 14;

- ▶ Discharge or not within 2 months after LT;
- ▶ Flow speed and volume of the portal vein at POD 3, 5, 7, 10 and 14;
- ▶ Ascites volume (mL/day) from abdominal drain at POD 3, 5, 7, 10 and 14.

Eligibility criteria

Inclusion

- ▶ Patients with end-stage liver disease who are scheduled to undergo LT
- ▶ Age ≥ 20 years at the time of registration
- ▶ Satisfies the indication criteria for LT at each participating institution
- ▶ Written informed consent provided to participate in the study

Exclusion

- ▶ Uncontrollable active infection other than liver
- ▶ Uncontrollable malignant diseases other than hepatocellular carcinoma
- ▶ Clinically problematic dysfunction of other organs
- ▶ Likely to have severe intra-abdominal adhesion due to a history of surgeries or past history of mechanical ileus
- ▶ Medication with antipsychotic, antidepressant or gastrointestinal prokinetic drugs
- ▶ Patients who take other Kampo medicines
- ▶ Women who are pregnant or lactating
- ▶ Any other medical condition that would render a patient unsuitable for inclusion according to the opinion of the investigator (at each institution).

Registration

An eligibility report form will be delivered to the registration centre at the Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital. Eligible patients will be centrally randomised to either Arm A (TJ-100) or Arm B (placebo) in accordance with the minimisation method for assigning patients to Arm A or Arm B according to the type of LT (LDLT or DDLT), body weight (<60 or ≥ 60 kg), age (<50 or ≥ 50 years) and the institution as variables before LT. Information regarding required follow-up evaluations will then be sent from the registration centre at the Institute for Advancement of Clinical and Translational Science.

The randomisation list will not be known in advance by the investigators. The statistical analysis and preparation of tables and graphs for the report of the study by the statistician of the study will be blinded to the extent possible. The unblinding may take place only after all data have been entered into the database of the study, all requests have been closed and the database has been frozen by the Data Manager of the study.

Treatment methods

Arm A: TJ-100 group

TJ-100 (5 g in solution) will be administered either orally or enterally via a tube three times per day

immediately before meals or every 8 h for 14 consecutive days between POD 1 and 14.

Arm B: placebo group

Placebo (5 g in solution) will be administered either orally or enterally via a tube three times per day immediately before meals or every 8 h for 14 consecutive days between POD 1 and 14.

TJ-100 and a matching placebo were manufactured by Tsumura & Co (Tokyo, Japan).

We monitor adherence by hearing each patient and checking the number of trial drugs (TJ-100 or placebo) that are not administered.

Prohibited or permitted drugs

Prohibited drugs: drugs that are known to promote bowel movement are prohibited during the protocol treatment: erythromycin, acetylcholine chloride, itopride hydrochloride, mosapride citrate, aclatonium nepadisilate, neostigmine methylsulfate, pantethine, panthenol, prostaglandin F_{2α}, proslutiamine, fursultiamine, trimebutine maleate, amidotrizoate sodium meglumine.

Permitted drugs: metoclopramide or domperidone to treat postoperative nausea/vomiting, and immunosuppressants including tacrolimus, cyclosporine, steroid, azathioprine, mizoribin and mycophenolate mofetil.

Criteria for discontinuing the protocol treatment

Grade 3 postoperative diarrhoea or other clinical adverse effects (CTCAE V.4.0 criteria).

Data collection

Prospective data about all patients including medical history, physical findings, laboratory findings, perioperative clinical information and complications will be collected.

Study design and statistical analysis

The primary end points will be statistically evaluated at POD 7 (total oral or enteral caloric intake, abdominal distension and abdominal pain determined using NRS).

The multiplicity issue (inflation of type I error) due to the analysis of three end points will be addressed using the fixed-sequence testing method. The order of the tests will be fixed, which controls the familywise error rate. The testing procedure will start from a hypothesis about the total oral and enteral caloric intake, and will be followed by the NRS for abdominal distension and the NRS for abdominal symptoms in that order. Each test will proceed only if all previously tested hypotheses have been rejected. Each hypothesis will be tested at the 5% significance level. The sample size was calculated on the basis of our previous finding that the mean value of the total oral and enteral caloric intake at POD 7 without the administration of TJ-100 is about 1000 kcal/day (SD=850) (unpublished data). We speculated that patients administered with TJ-100 would have an intake of 500 kcal/day more than those who were not administered with TJ-100. Thus, assuming that the two arms

have the same SD, the sample size was calculated on the basis of a t test with a two-sided significance level of 5% and a power of 80%, which resulted in a requirement of 47 patients per group. Taking about 15% exclusion from analysis into account, the number of patients to be accrued was set at 55 per treatment arm (110 in total). If the sample for analyses is 47 per group and the two-sided significance level is 5%, and if the probability of an event in which the value of the NRS in Arm A is larger than that in Arm B is about 0.62, then the Wilcoxon rank-sum test would have an approximate power of 80% for each NRS test of abdominal distension and abdominal symptoms. The first primary end point, the total oral and enteral caloric intake at POD 7, will be compared between the two treatment groups using the t test. The second and the third primary end points, the values of NRS on abdominal distension and abdominal pain, will be compared between the two treatment groups using the Wilcoxon rank-sum test. When the total oral and caloric enteral intake data at POD 7 for 50 patients are collected, we will conduct an interim analysis to confirm the distribution of total oral and enteral caloric intake at POD 7 under double-blind conditions. If the distribution obviously deviates from the normal distribution, then the Wilcoxon rank-sum test will be used for the primary analysis of the total oral and enteral caloric intake at POD 7.

Participating institutions

Fourteen leading Japanese institutions that perform LT will participate in this trial.

Registration of the protocol

The protocol was approved by the institutional review board of each participating institute and conducted in accordance with the Declaration of Helsinki of 1996. Written informed consent will be obtained from all patients before enrolment and randomisation by investigators. The DKB 14 Study was registered in the University Hospital Medical Information Network Clinical Trial Registration (UMIN-CTR), Japan (registration number: UMIN000014326) during 2014.

Study status

This study is currently collecting data and there has not been any publication concerning the analysis of the data collected to date.

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Contributors TK and SU conceived the study. All the authors were involved in development of the study protocol. TK prepared the first draft of the manuscript and all the authors critically reviewed, revised and approved the subsequent and final version.

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Competing interests None declared.

Ethics approval The protocol was approved by the institutional review board of each participating hospital.

Patient consent Obtained.

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