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ORIGINAL ARTICLE

A prospective single-institute study of the impact of Daikenchuto on the early postoperative outcome after living donor liver transplantation☆,☆☆

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Summary *Background:* The aim of this study was to investigate the impact of Daikenchuto (DKT) on early postoperative outcomes after living donor liver transplantation (LDLT), focusing on the prevention of abdominal distension and bacterial translocation.
Methods: Adult LDLT recipients were prospectively divided into 2 groups, who were administered DKT (n = 20, group A) or not (n = 20, group B). The area of bowel gas defined as gas volume score (GVS) 7 days after LDLT was calculated. Postoperative liver function tests, the development of bacterial, viral, and fungal infections, and GVS after LDLT were reviewed.
Results: There were no significant differences in liver function tests and ammonia level after LDLT. Also, the rates of infection and the result of culture study were not different between groups. The median GVS 7 days after LDLT was not significantly different between groups A (0.26 (range, 0.12–0.58)) and B (0.23 (range, 0.15–0.42)).
Conclusions: No positive impact was observed for 14-day DKT administration after LDLT, in terms of preventing infection or abdominal distension.

Abbreviations and acronyms: DKT, Daikenchuto; LDLT, living donor liver transplantation; GVS, gas volume score; CMV, cytomegalovirus; C-LC, hepatitis C virus cirrhosis; B-LC, hepatitis B virus cirrhosis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; FHF, fulminant hepatic failure; LOHF, late-onset hepatic failure; HCC, hepatocellular carcinoma; GV, graft volume; RSLV, recipient standard liver volume; MELD, model for end-stage liver disease; CRP, C-reactive protein.

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☆☆ This study was approved by an institutional review board in Nagasaki University Hospital (approval number 11062778; UMIN ID 000013530).

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1. Background

Daikenchuto (DKT) is an herbal drug well known to activate intestinal motility. Numerous studies have shown the efficacy of DKT at improving bowel diseases, including ileus, Crohn's disease and radiation-induced enteritis.[1–3] Previously, we showed the efficacy of DKT at increasing portal flow in rats after liver surgery[4]; Ogasawara et al observed the same effect in a clinical setting after LDLT.[5] While activating intestinal motility and portal flow, DKT might be effective at preventing not only abdominal distension, but also bacteremia due to bacterial translocation from intestine. Although Yoshikawa et al reported the efficacy of DKT at preventing bacterial translocation in rats,[6] no study has been done on clinical liver transplantation.

The aim of this study was to show the impact of DKT on the early postoperative outcome after LDLT, focusing on the prevention of abdominal distension and infection including bacterial translocation.

2. Material and methods

2.1. Patients

Forty adult LDLT patients older than 16 years were prospectively divided into 2 groups, either administered DKT (n = 20, group A) or not (n = 20, group B). In group A, DKT was administered at 5.0 g three times a day, from day 1 to day 14 after LDLT, first via the enteral feeding tube placed at the jejunum during surgery, then by oral intake. In group B, the same dose of saline not including DKT was given as the control, and other postoperative management was identical to that of group A, as described later. The characteristics of the patients are summarized in Table 1. This study was approved by an institutional review board in Nagasaki University Hospital (approval number 11062778; UMIN ID 000013530), and all patients provided fully informed consent.

2.2. Postoperative management

The surgical procedure has been described elsewhere.[7] The basic immunosuppression consisted of tacrolimus and steroid. Mycophenolate mofetil was used for cases with renal dysfunction. Post-transplant antibiotic prophylaxis consisted of cefazolin and ampicillin at 1 g each, four times a day, for 3 days after LDLT. Continuous enteral feeding was started the day after surgery via the catheter placed in jejunum during surgery, using a fat-free elemental diet (Elental®, Ajinomoto Pharmaceutical Co. Ltd, Tokyo, Japan). It was discontinued after the patients demonstrated sufficient oral intake ability.

2.3. Definition of the infections

After transplantation surgery, samples were obtained weekly from the nares, respiratory secretions, urine, stool, ascites, and bile (when applicable) of each patient as surveillance cultures. Bacterial infections were defined as follows. Bacteremia was defined as the isolation of bacteria in at least one blood culture with obvious clinical signs of infection (high fever and/or elevation of serum level of C-reactive protein). Pneumonia was defined as a new

Table 1 Characteristics of the patients.

	Group A (DKT(+)) n = 20	Group B (DKT(−)) n = 20	
Age	59 (26–70)	60 (24–69)	NS
Gender	M14/F6	M12/F8	NS
Diagnoses			
C-LC	5 (3 with HCC)	7 (4 with HCC)	
B-LC	4	0	
NBNC-LC	2	3	
Alcoholic LC	5	6 (3 with HCC)	NS
PBC	2	1	
PSC	1	1	
FHF	1	1	
LOHF	0	1	
Liver graft			
Right lobe	10	7	NS
Extended left lobe	10	13	
GV/RSLV (%)	47.5 (31.1–70.3)	45.0 (28.9–73.9)	NS
MELD	15 (8–27)	14 (8–33)	NS
Blood type combination			
Identical/Compatible	14	16	NS
Incompatible	6	4	
Duration of surgery (minutes)	787 (597–1031)	721 (577–897)	NS
Blood loss (g)	6550 (2600–16,300)	5350 (2050–30,500)	NS
Biliary reconstruction			
Duct-to-Duct	19	19	NS
Hepaticojejunostomy	1	1	
Splenectomy	10	10	NS

Data are presented as median (range).
C-LC, hepatitis C virus cirrhosis; B-LC, hepatitis B virus cirrhosis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholaingitis; FHF, fulminant hepatic failure; LOHF, late-onset hepatic failure; HCC, hepatocellular carcinoma; GV, graft volume; RSLV, recipient standard liver volume; MELD, model for end-stage liver diseases

pulmonary infiltrate developed on radiographic studies in conjunction with clinical signs of purulent sputum, with bacteria isolated from respiratory secretion. Cholangitis was defined as the elevation of serum bilirubin, and the isolation of bacteria in bile obtained from biliary drainage with clinical signs of infection. Peritonitis was diagnosed if bacteria were isolated from ascites obtained intra- or post-operatively with clinical signs of infection. Wound infection was defined as the isolation of bacteria from a purulent fluid drained from the wound. Cytomegalovirus (CMV) infection was defined as positive CMV-antigenemia,[8] and fungal infection was defined as identification of fungus in a culture study and/or clinical signs of infection with high β-glucan level.[9]

2.4. Measurement of abdominal gas

The area of abdominal gas on X-ray, 7 days after LDLT was calculated with Image J software (free download from http://rsbweb.nih.gov/ij/) according to the procedure introduced by Koide et al.[10] Briefly, with the digital data of abdominal X-ray in the supine position, the pixel value of abdominal gas area was calculated after being traced by hand, and the gas volume score (GVS) was defined as the whole area of the traced abdominal gas divided by the area surrounded by a horizontal line tangential to the supra-symphysary margin, a horizontal line tangential to the up-permost diaphragm, and the most lateral line tangential to the right and left costal arches.

2.5. Statistical analyses

Data are presented as medians (ranges). Student's t test was used for comparisons of continuous variables, and the chi-square test or Fisher's test was used for categorical variables. A p value of <0.05 was considered statistically significant. Statistical analysis was performed with GraphPad Prism 6 for Windows (GraphPad Software, Inc., San Diego, USA).

3. Results

3.1. Postoperative liver function tests, ammonia level and inflammatory markers after LDLT

At 7 days after LDLT, there were no significant differences in the median levels of alanine aminotransferase (110 IU/L (range, 24–242) in group A vs 83 IU/L (26–332) in group B, P = 0.44), total bilirubin (4.9 mg/dl (range, 2.0–16.8) in group A vs 4.4 mg/dl (0.9–10.1) in group B, P = 0.07) and prothrombin time (73% (range, 41–96) in group A vs 83% (27–114) in group B, P = 0.25) 7 days after LDLT. Also, there was no significant difference in ammonia level (20 μg/dl (range, 10–79) in group A vs 21 μg/dl (10–120) in group B, P = 0.26) and C-reactive protein (CRP) (1.35 mg/dl (range, 0.39–9.52) in group A vs 0.86 mg/dl (0.22–11.09) in group B, P = 0.36) between the groups.

3.2. Postoperative infections after LDLT

Twelve episodes of bacterial infection occurred in 10 group A patients (50%), while 16 episodes occurred in 13 group B patients (65%) (Table 2). There was no significant difference in the incidence of bacterial infections between groups A and B. In terms of bacterial translocation, bacteria generally derived from the bowel were equally identified in the blood cultures in groups A and B (2 cases of *E. cloacae* in group A; 1 case each of *E. faecalis* and *E. Coli* in group B). Other bacteria detected in blood culture was 2 cases of *P. aeruginosa* in group A, possibly derived from the central vein catheter, because same bacteria was identified from the catheter. Also, there were no significant differences between groups in the incidence of CMV infection (6/20 (30%) in group A vs 10/20 (50%) in group B, P = 0.33) or fungal infection (1/20 (5%) in group A vs 3/20 (15%) in group B, P = 0.29).

Table 2 Bacterial infections after LDLT.

	Group A n = 20	Group B n = 20	
Bacteremia	4	2	NS
Respiratory	2	3	NS
Enteritis	0	1	NS
Cholangitis	1	3	NS
Surgical site infection			
Pancreatic fistula	1	1	NS
Peritonitis	2	2	NS
Urinary	2	4	NS

3.3. Postoperative GVS after LDLT

GVS values at 7 days after LDLT were not significantly different between groups, with 0.26 (range, 0.12–0.58) for group A and 0.23 (0.15–0.42) for group B (Fig. 1). Also,

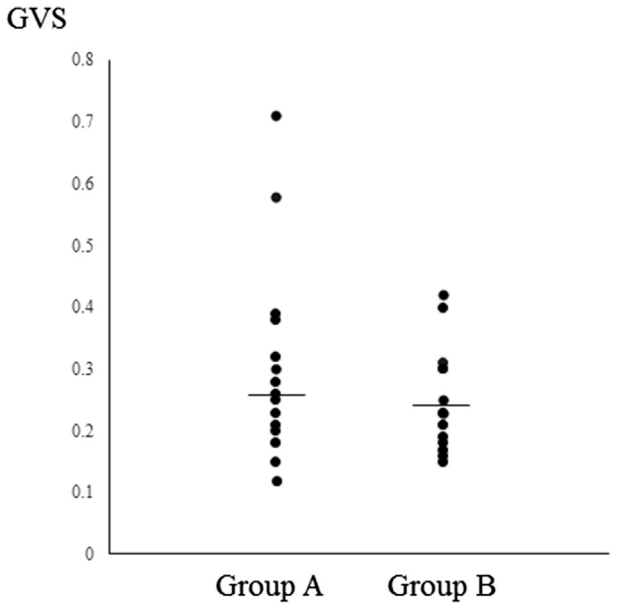

Figure 1 Gas volume score (GVS), 7 days after LDLT. There was no significant difference between group A (DKT (+)) and group B (DKT (−)).

there was no significant difference in median postoperative first-day defecation between the groups (6 (range, 4—10 day) in group A vs 7 (3—11) in group B).

3.4. In-hospital mortality after LDLT

There was no significant difference in in-hospital mortality after LDLT between the groups: 1/20 (5%) for group A and 0/20 (0%) in group B. One patient in group A died of severe hepatitis C virus recurrence, 166 days after LDLT.

4. Discussion

DKT is an herbal drug mixture composed of 4 ingredients: Japanese pepper extract, processed ginger, ginseng radix, and maltose powder derived from rice. DKT is well known to stimulate intestinal motility with its action both on sensory neurons of the gut and on non-neuronal tissues,[11] and it has been shown to improve several bowel diseases clinically, as mentioned before. DKT also has several positive impacts on the physiology of the liver, including the increase of portal venous flow[4,5] and prevention of sinusoidal obstruction syndrome.[12] Additionally, DKT has an anti-inflammatory effect traced to several mechanisms including suppression of TNF-α and activation of nicotinic acetylcholine receptors in the postoperative ileus.[13] In clinical liver surgery, Nishi et al reported that DKT has an anti-inflammatory function with a low level of CRP and β-D glucan after hepatectomy.[14] Yoshikawa et al reported that DKT contributed to preventing inflammation of the intestine, while maintaining the microbiome of rats under fasting stress,[15] and DKT is effective at preventing bacterial translocation in a rat model of hepatectomy.[6] They showed that DKT contributed to maintaining intestinal integrity, preventing villus apoptosis under fasting stress. Bacterial translocation is one of the life-threatening complications after liver transplantation, but the efficacy of DKT has not been elucidated in the clinical situation.

Based on the reported efficacy of DKT, we aimed to clarify its impact on the early outcome after LDLT, but our study could find no positive results in terms of the prevention of abdominal distension and infection. Abdominal gas was calculated 7 days after LDLT, and there was no significant difference between the groups with and without DKT treatment. As we mentioned before, we followed the procedure of measuring bowel gas as GVS introduced by Koide et al.[10] In the study by Koide et al, they showed that GVS measured by their method was significantly greater in cases of irritable bowel syndrome than in normal controls. The median GVS after LDLT in our study was generally high, at 0.26 in the DKT-treated group and 0.23 in the control group, compared to the study by Koide et al, which had a mean GVS of 0.069 in irritable bowel disease, possibly because of the generally insufficient bowel movement in the early postoperative period in our series. Because it is difficult to evaluate the subjective complaint of abdominal distension, especially just after LDLT, we adopted the GVS as the objective index. However, on hindsight it might be better to evaluate other objective findings of bowel motility, including first-day flatus or defecation after surgery. Actually, we could not find any differences in the first-day defection after transplantation. Also, the timing of majoring GVS is also debatable issue. Because of that the first-day defecation after transplantation was not significantly different between the groups around 1 week, we believe that the timing of majoring GVS 1 week after transplantation was appropriate. However, it might be better to check GVS serially, to prove actual bowel movement in early period after transplantation.

Also in terms of the prevention of infection, we could not show a positive impact of DKT on bacterial, CMV or fungal infection after LDLT. Even with regard to bacterial translocation, bacteria derived from the bowel were equally identified in the blood culture of patients with or without DKT treatment. As mentioned before, Yoshikawa et al showed the importance of maintaining intestinal integrity with DKT to prevent bacterial translocation under fasting stress.[6] Because we introduced an elementary diet just after LDLT in both groups, the intestinal integrity was maintained, and villus apoptosis might have been avoided regardless of whether DKT was administered. Several studies have shown the importance of alterations in microbiota in liver diseases, especially in decompensated liver cirrhosis.[16] These findings informed our hypothesis that DKT would have a positive impact on the postoperative outcome after liver transplantation by controlling intestinal motility and inflammation: i.e., that it would help deal with the dramatic change of microbiota accompanying the change from the cirrhotic to normal-liver environment. Accordingly, when it is difficult to introduce the elementary diet early after liver transplantation, DKT might be effective to avoid the bacterial translocation with maintaining intestinal integrity.

There are several limitations in this study, mainly the small number of cases. It should require much more cases especially to clarify the efficacy of DKT on the outcome of bacteremia due to bacterial translocation, because the incidence of such case is generally not so high. Because this study is performed as the pilot study in a single institution, a prospective and randomized multicenter trial with a large case number will be required to make further progress on this issue. Also, the optimal protocol of DKT administration after LDLT is an important issue yet to solve, because the small volume of the partial liver might affect the portal system.

In conclusion, DKT showed no positive impact on the early outcome after LDLT in terms of the prevention of abdominal distension and infections, in a Japanese single institute.

Conflict of interest

No authors have a conflict of interest to declare in this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2017.12.003.

References

1. Itoh T, Yamakawa J, Mai M, Yamaguchi N, Kanda T. The effect of the herbal medicine dai- kenchu-to on post-operative ileus. *J Int Med Res*. 2002;30:428—432.

2. Kanazawa A, Sako M, Takazoe M, et al. Daikenchuto, a traditional Japanese herbal medicine, for the maintenance of surgically induced remission in patients with Crohn's disease: a retrospective analysis of 258 patients. *Surg Today*. 2014;44:1506—1512.
3. Takeda T, Kamiura S, Kimura T. Effectiveness of the herbal medicine daikenchuto for radiation-induced enteritis. *J Altern Complement Med*. 2008;14:753—755.
4. Muraoka I, Takatsuki M, Soyama A, et al. Efficiency of herbal medicine Dai-kenchu-to on portal blood flow in rat models. *Ann Med Surg (Lond)*. 2015;4:211—214.
5. Ogasawara T, Morine Y, Ikemoto T, et al. Influence of Dai-kenchu-to (DKT) on human portal blood flow. *Hepatogastroenterology*. 2008;55:574—577.
6. Yoshikawa K, Kurita N, Higashijima J, et al. Kampo medicine "Dai-kenchu-to" prevents bacterial translocation in rats. *Dig Dis Sci*. 2008;53:1824—1831.
7. Eguchi S, Takatsuki M, Hidaka M, Tajima Y, Kanematsu T. Evolution of living donor liver transplantation over 10 years: experience of a single center. *Surg Today*. 2008;38:795—800.
8. Yamanouchi K, Eguchi S, Takatsuki M, et al. Management of cytomegalovirus infection after living donor liver transplantation. *Hepatogastroenterology*. 2012;59:231—234.
9. Yamanouchi K, Takatsuki M, Hidaka M, Soyama A, Kanematsu T, Eguchi S. Significance of serum β-D-glucan levels in recipients of living donor liver transplantation. *J Hepatobiliary Pancreat Sci*. 2011;18:432—435.
10. Koide A, Yamaguchi T, Odaka T, et al. Quantitative analysis of bowel gas using plain abdominal radiograph in patients with irritable bowel syndrome. *Am J Gastroenterol*. 2000;95:1735—1741.
11. Kono T, Kanematsu T, Kitajima M. Exodus of Kampo, traditional Japanese medicine, from the complementary and alternative medicines: is it time yet? *Surgery*. 2009;146:837—840.
12. Narita M, Hatano E, Tamaki N, et al. Dai-kenchu-to attenuates rat sinusoidal obstruction syndrome by inhibiting the accumulation of neutrophils in the liver. *J Gastroenterol Hepatol*. 2009;24:1051—1057.
13. Endo M, Hori M, Ozaki H, Oikawa T, Hanawa T. Daikenchuto, a traditional Japanese herbal medicine, ameliorates postoperative ileus by anti-inflammatory action through nicotinic acetylcholine receptors. *J Gastroenterol*. 2014;49:1026—1039.
14. Nishi M, Shimada M, Uchiyama H, et al. The beneficial effects of Kampo medicine Dai-ken-chu-to after hepatic resection: a prospective randomized control study. *Hepatogastroenterology*. 2012;59:2290—2294.
15. Yoshikawa K, Shimada M, Kuwahara T, et al. Effect of Kampo medicine "Dai-kenchu-to" on microbiome in the intestine of the rats with fast stress. *J Med Invest*. 2013;60:221—227.
16. Qin N, Yang F, Li A, et al. Alterations of the human gut microbiome in liver cirrhosis. *Nature*. 2014;513:59—64.