questionnaire showed recovery of both the PCS summary score and the BP pain score by 6 months after operation. Considering the previous report of evaluation of living liver donors by the SF36-v2 questionnaire [20], recovery from bodily pain and physical disturbance after surgery was quicker in the LADH group than in the ODH group. These results showed that LADH may be less invasive and have a positive impact on the postoperative QOL in the donors.

The graft survival rates in the recipient patients, which were fundamental and important in evaluating the outcome of donor hepatectomy, were similar between the LADH group and the ODH group either in left lateral sectionectomy or left lobe resection. The slight difference in the graft survival rates between the LADH-left and the ODH-left groups in left lobe resection was considered to have resulted in part because of the different time periods in which the surgeries had been performed. These results could also strengthen the positive evaluation of the LADH procedure from the standpoint not only of the donors but also the recipients.

This study was not a randomized or high-volume study. Therefore, the results should be interpreted cautiously. Nonetheless, the results suggesting that LADH was safe and feasible, and provided a better QOL after surgery in our series, may justify continuation of LADH for procuring left liver grafts.

One of the problems in our series was that the operative time for procuring a left liver graft with LDAH was significantly longer than that of open surgery. The operative time for left-lobe LADH depends on the duration of open procedures, suggesting that more experience in hilar dissection and parenchymal transection under the hybrid procedure would be important for reducing the operative time. Another approach could be increasing the length of the incision to more than 10 cm, especially in donors with an RPv distance of more than 10 cm.

In conclusion, LADH was safe and feasible for harvesting left liver grafts in the hands of surgeons with experience in both open donor surgery and laparoscopic surgery, and use of the procedure had a positive impact on the postoperative QOL in the donors, although the prolonged duration of the procedure in the LADH-left group needs to be improved with further experience and improvements in the technique of LADH. Left-lobe LADH should be carefully planned in donors with an RPv distance of more than 10 cm, in view of the potential surgical difficulty.

References

1. Akabayashi A, Slingsby BT, Fujita M (2004) The first donor death after living-related liver transplantation in Japan. Transplantation 77:634
2. Miller C, Florman S, Kim-Schluger L et al (2004) Fulminant and fatal gas gangrene of the stomach in a healthy live liver donor. Liver Transpl 10:1315–1319
3. Surman OS (2002) The ethics of partial-liver donation. N Engl J Med 346:1038
4. Umeshita K, Fujiwara K, Kiyosawa K et al (2003) Operative morbidity of living liver donors in Japan. Lancet 362:687–690
5. Hashikura Y, Ichida T, Umeshita K et al (2009) Donor complications associated with living donor liver transplantation in Japan. Transplantation 88:110–114
6. Cherqui D, Soubrane O, Husson E et al (2002) Laparoscopic living donor hepatectomy for liver transplantation in children. Lancet 359:392–396
7. Koffron AJ, Kung R, Baker T et al (2006) Laparoscopic-assisted right lobe donor hepatectomy. Am J Transplant 6:2522–2525
8. Nguyen KT, Marsh JW, Tsung A et al (2011) Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. Arch Surg 146:348–356
9. Kurosaki I, Yamamoto S, Kitami C et al (2006) Video-assisted living donor hemihepatectomy through a 12-cm incision for adult-to-adult liver transplantation. Surgery 139:695–703
10. Suh KS, Yi NJ, Kim T et al (2009) Laparoscopy-assisted donor right hepatectomy using a hand port system preserving the middle hepatic vein branches. World J Surg 33:526–533. doi:10.1007/s00268-008-9842-z
11. Baker TB, Jay CL, Ladner DP et al (2009) Laparoscopy-assisted and open living donor right hepatectomy: a comparative study of outcomes. Surgery 146:817–823
12. Nitta H, Sasaki A, Fujita T et al (2010) Laparoscopy-assisted major liver resections employing a hanging technique: the original procedure. Ann Surg 251:450–453
13. Kim KH, Jung DH, Park KM et al (2011) Comparison of open and laparoscopic live donor left lateral sectionectomy. Br J Surg 98:1302–1308
14. Takayama T, Makuuchi M, Kubota K et al (2000) Living-related transplantation of left liver plus caudate lobe. J Am Coll Surg 190:635–638
15. Kokudo N, Sugawara Y, Kaneko J et al (2004) Reconstruction of isolated caudate portal vein in left liver graft. Liver Transpl 10:1163–1165
16. Marubashi S, Nagano H, Wada H et al (2011) Donor hepatectomy for living donor liver transplantation: learning steps and surgical outcome. Dig Dis Sci 56:2482–2490
17. Koffron AJ, Kung RD, Auffenberg GB et al (2007) Laparoscopic liver surgery for everyone: the hybrid method. Surgery 142:463–468
18. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6,336 patients and results of a survey. Ann Surg 240:205–213
19. Clavien PA, Strasberg SM (2009) Severity grading of surgical complications. Ann Surg 250:197–198
20. Togashi J, Sugawara Y, Tamura S et al (2011) Donor quality of life after living donor liver transplantation: a prospective study. J Hepatobiliary Pancreat Sci 18:263–267
21. Tsamis D, Theodoropoulos G, Stamopoulos P et al (2012) Systemic inflammatory response after laparoscopic and conventional colectomy for cancer: a matched case-control study. Surg Endosc 26:1436–1443

World J Surg (2013) 37:2671–2677
DOI 10.1007/s00268-013-2188-1

World Journal of Surgery

Hepatic Artery Reconstruction in Living Donor Liver Transplantation: Risk Factor Analysis of Complication and a Role of MDCT Scan for Detecting Anastomotic Stricture

Shigeru Marubashi · Shogo Kobayashi · Hiroshi Wada · Koichi Kawamoto · Hidetoshi Eguchi · Yuichiro Doki · Masaki Mori · Hiroaki Nagano

Published online: 28 August 2013

Abstract

Background In partial liver transplantation, reconstruction of the hepatic artery is technically highly demanding and the incidence of arterial complications is high. We attempted to identify the risk factors for anastomotic complications after hepatic artery reconstruction and examined the role of multidetector-row computed tomography (MDCT) in the evaluation of the reconstructed hepatic artery in liver transplant recipients.

Methods A total of 109 adult-to-adult living donor liver transplantations (LDLT) were performed at our institute between 1999 and July 2011. Hepatic artery reconstruction was performed under a surgical microscope (MS group, $n = 84$), until we began to adopt surgical loupes (4.5×) for arterial reconstructions in all cases after January 2009 (SL group, $n = 25$). A dynamic MDCT study was prospectively carried out on postoperative days 7, 14, and 28, and at postoperative month 3, 6, and 12 after April 2005 ($n = 60$).

Results There were no cases of hepatic artery thrombosis and six cases (5.5 %) of interventional radiology-confirmed hepatic artery stenosis (HAS). Risk factor analysis for HAS showed that ABO-incompatible LDLT was associated with HAS. Use of surgical loupes provided superior results as compared to anastomosis under a surgical microscope, and it also provided the advantage of reduced operative time. The MDCT procedure was useful for detecting HAS; however, the false positive rate was relatively high until 3 months after the LDLT (100 % sensitivity and 72.8 % specificity at 3 months).

Conclusions Hepatic arterial anastomosis using surgical loupes tended to be time-saving and to yield similar or better results than traditional microscope-anastomosis. The use of MDCT aided the diagnosis of HAS, although the substantial false positive rate should be borne in mind in clinical practice.

Abbreviations

DUS	Doppler ultrasonography
HAS	Heoatic artery stenosis
IVR	Interventional radiology
LDLT	Living donor liver transplantation
MELD score	Model for end-stage liver disease score
MDCT	Multidetector-row CT
POD	Postoperative day
POM	Postoperative month
RI	Resistive index
SMA	Superior mesenteric artery

Introduction

Hepatic artery reconstruction is the most important surgical procedure for liver transplantation, and complications associated with this vascular reconstruction, such as hepatic artery thrombosis or stenosis, may have a significant influence on the recipients' prognosis. In partial liver transplantation, where the hepatic arterial system should be reconstructed using a branch of the hepatic artery, such as the right hepatic artery in right liver grafting and the left and middle hepatic arteries in left liver grafting, reconstruction of the hepatic artery is technically highly demanding and the incidence of arterial complications is

S. Marubashi (✉) · S. Kobayashi · H. Wada · K. Kawamoto · H. Eguchi · Y. Doki · M. Mori · H. Nagano
Department of Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: smarubashi@gesurg.med.osaka-u.ac.jp

high. The reported incidence of hepatic artery thrombosis is in the range of 3.1–22 %, and that of hepatic artery stenosis (HAS) is in the range of 4.8–24.6 % [1–7]. The anastomosis procedure using a surgical microscope, first introduced in the 1990s, aimed at better patency and a lesser degree of graft damage in partial liver transplantation [8, 9], and it has since become a standard technique in partial liver transplantation [10, 11]. However, anastomosis using surgical loupes is more popular in some programs because of its advantages over anastomosis using the surgical microscope, such as the time saved for adjusting the operative fields and better focusing in the abdominal cavity [12], with similar surgical outcomes [12–14]. Including comparative studies between the methods using the microscope and surgical loupes [12–14], very few studies have been conducted to investigate the risk factors for the development of hepatic arterial complications.

Doppler ultrasonography (DUS) is the current gold standard for evaluating hepatic arterial thrombosis and stenosis, both intraoperatively and postoperatively. Measurements of the resistive index of the reconstructed hepatic artery, the tardus–parvus waveform, or other useful parameters in a Doppler study have been shown to provide rather accurate diagnosis of HAS [6, 15–19]. Recently, multidetector row computed tomography (MDCT) has been demonstrated to be useful for the evaluation of small-arterial complications, obviating the need for the more invasive angiography, and to also be quite useful for the diagnosis of post-transplant complications [20, 21]. However, there is very little information so far about the usefulness of MDCT in the evaluation of the hepatic artery in liver transplant recipients [21, 22].

In the present study, we attempted to identify the risk factors for anastomotic complications after hepatic artery reconstruction, and examined the role of MDCT in evaluation of the reconstructed hepatic artery in liver transplant recipients.

Patients and methods

A total of 109 adult-to-adult living donor liver transplantations (LDLT), including one re-transplantation, were performed at our institute between 1999 and July 2011; the total of 108 transplant recipients comprised 57 male and 51 female patients, with a mean age of 49.8 ± 12.3 years. The indications for liver transplantation consisted of viral cirrhosis ($n = 67$), cholestatic liver disease ($n = 14$), fulminant liver failure ($n = 8$), and others ($n = 20$). Among the 109 liver transplantations, 7 transplants were ABO-incompatible. The liver grafts consisted of the right lobe in 61 cases, left lobe with or without the caudate in 38 cases, and the right posterior section in 10 cases.

Surgical techniques

Hepatic artery reconstruction was performed under a surgical microscope (OPMI Vario S88, Zeiss, Tokyo, Japan) (MS group, $n = 84$) until January 2009, when we began to adopt surgical loupes (4.5×, Zeiss, Tokyo, Japan) for arterial reconstructions in all cases (SL group, $n = 25$).

The procedures for anastomosis were similar between the MS and SL groups. First, the hepatic artery in both the donor and the recipient was carefully handled, with appropriate preservation of the surrounding connective tissue, so as to avoid skeletonization of the artery. Appropriate alignment of both the length and rotation was determined. End-to-end anastomosis was carried out by interrupted sutures using non-absorbable monofilament 8-0 (polypropylene suture). First, both the dorsal and ventral ends were anastomosed. While the sutures were stretched apart gently by the first assistant, three to four sutures were placed on one side and tied after confirmation of their correct placement through the arterial layers. The other side was then sutured after flipping the artery, keeping the two angle sutures stretched. If there were multiple arteries in the donor liver, all of the arteries were anastomosed, to the extent feasible.

All the surgical procedures were undertaken by two experienced hepatobiliary transplant surgeons.

Immediately after reperfusion of the liver, DUS was performed. Values of the resistive index of the hepatic artery in the liver hilum of less than 0.6 or peak arterial velocity values of less than 15 cm/s at the proximal part of the intrahepatic artery are considered as abnormal, and the anastomosis was always repeated if the intraoperative DUS study was abnormal.

Postoperative anticoagulant therapy

We routinely start standard anticoagulant therapy once the patient's postoperative condition has stabilized. Intravenous administration of heparin sodium is initiated at the dose of 100 U/h when the aPTT (abnormal partial thromboplastin time) is lower than 40 s. When the target aPTT increased to the range of 40–50 s, then the heparin sodium dose was titrated and could be increased to 600 U/h until postoperative day (POD) 28. The anticoagulant therapy was usually discontinued on POD 28; however, if any abnormality was detected on DUS or MDCT, it was continued beyond POD 28. Antiplatelet agents were started for interventional radiology (IVR)-confirmed or DUS-diagnosed HAS until the abnormality improved or resolved. At this point, warfarin was initiated, with the target prothrombin time/international normalized ratio (PT-INR) set at 1.5–2.5, for any portal venous or hepatic venous abnormalities, such as partial thrombosis.

Postoperative evaluation of the hepatic artery anastomosis

Doppler ultrasound was routinely performed twice a day in the immediate postoperative period (until POD 3), with the frequency of the study reduced to once daily until POD 28, and thereafter to once every other day, and finally to once a week during the remaining period of the patient's hospital stay. In addition, diagnostic DUS was also performed anytime in the event of elevation of the serum transaminase levels. The abnormal findings of hepatic artery anastomosis that were considered as warranting hepatic arterial angiography and IVR consisted of the combination of a refractive index (RI) value of less than 0.6 in the DUS study and elevation of the serum AST or ALT (DUS-based criteria).

Interpretation of the CT images was performed by expert radiologists on staff in the hospital. Hepatic arterial complications were classified by these experts into four categories; (1) hepatic arterial thrombosis; (2) hepatic arterial stenosis, defined as anastomotic narrowing of >50 %; (3) suspected or mild hepatic arterial stenosis, defined as anastomotic narrowing of less than 50 %; and (4) normal findings. In April 2005 MDCT was introduced in our hospital; before that date CT had been performed whenever needed for diagnosing suspected hepatic arterial complications. After April 2005, we started prospective dynamic MDCT studies in recipients of liver transplants ($n = 60$), in which dynamic MDCT was performed in the recipients on POD 7, 14, 28, and at postoperative month (POM) 3, 6, and 12.

In contrast to the absolute indication of angiography/IVR in cases fulfilling DUS-based criteria, abnormal findings such as suspected hepatic arterial stenosis on CT or MDCT alone, in the absence of DUS-based criteria, are not considered clinically significant; therefore IVR was not performed. We defined IVR-confirmed HAS cases as those in which the HAS was confirmed by angiography, and control cases as those not fulfilling the DUS-based criteria.

Risk factor analysis for HAS and evaluation of the role of MDCT

To identify the risk factors for the development of HAS, the following factors were analyzed and compared between the IVR-confirmed HAS group ($n = 6$) and the control group not fulfilling the DUS-based criteria for HAS ($n = 101$): recipient age, preoperative model for end-stage liver disease score (MELD score), donor age, donor arterial diameter, number of anastomoses, anastomosis method (microscope versus surgical loupes), time for anastomosis, graft type (right lobe, left lobe, right lateral sector), ABO incompatibility between donor and recipient, and presence/absence of acute rejection.

Furthermore, the usefulness of MDCT in the diagnosis of hepatic arterial complications was investigated in the participants of the prospective MDCT study ($n = 60$). The MDCT findings were compared between the IVR-confirmed HAS group ($n = 3$) and the control group not fulfilling the DUS-based criteria for HAS ($n = 57$).

Statistical analysis

Results are expressed as mean ± standard deviation. Statistical examination of the correlations was based on the Pearson's product-moment correlation. Clinical data of the donors were compared with Student's t test. P values less than 0.05 were considered to indicate statistical significance.

Results

The patient characteristics and summary of the hepatic anastomosis procedure are described in Table 1. The patient background characteristics were similar between the MS group ($n = 85$) and the SL group ($n = 24$). With regard to the graft type, the frequency of right lobe grafts, as compared to left lobe and other grafts, tended to be higher in the MS group than in the SL group, and the graft weight/recipient standard liver volume (GW/SLV) ratio was larger in the MS group than in the SL group ($P = 0.036$ for both). The cold ischemia time was significantly longer in the SL group, while the warm ischemia time was shorter in the SL group than that in the MS group ($P = 0.0001$ and 0.029, respectively). The patient survival curves of the SL and MS groups are shown in Fig. 1. Survival in the SL group was better than in the MS group, although the difference did not reach statistical significance ($P = 0.057$, log rank test).

A single hepatic artery anastomosis was performed in 96 patients (88.1 %), while double anastomoses were performed in 12 cases (11.0 %) and a triple anastomosis was needed in 1 case (0.9 %). The diameter of the main hepatic artery was similar between the MS and SL groups. None of the 109 patients developed the complication of hepatic artery thrombosis, but HAS was diagnosed according to DUS-based criteria in 8 patients (7.3 %); of those eight patients, all of whom went on to have IVR, the diagnosis was confirmed by IVR in 6 (5.5 %). Treatment with percutaneous transarterial balloon dilatation was successful in two cases, whereas failure due to an intimal flap occurred in one case (12.5 %). In another three cases, treatment was not indicated because of technical difficulties, such as meandering proximal artery or arterial spasm (37.5 %). The two cases with HAS diagnosed according to DUS-based criteria alone had trivial stenosis that did not warrant

Table 1 Patient characteristics

	Total ($n = 109$)	Microscope (MS group) ($n = 85$)	Surgical loupes (SL group) ($n = 24$)	P value
Recipient age	49.8 ± 12.3	49.1 ± 12.5	53.1 ± 11.1	0.231
Recipient gender (M/F)	58/51	48/37	10/14	0.199
Indication (viral/cholestatic/fulminant/others)		54/13/9/18	15/5/2/3	0.766
PreOP MELD score	20.7 ± 8.9	20.8 ± 9.0	20.2 ± 8.8	0.865
Donor age	38.1 ± 13.2	38.1 ± 13.1	38.1 ± 13.1	0.953
Donor gender				
Blood type (identical/compatible/incompatible)	76/26/7	57/23/5	19/3/2	0.328
Graft type (right/left/right lateral)	61/38/10	50/25/10	11/13/0	0.036
Graft weight/standard liver volume (%)	48.4 ± 10.2	49.4 ± 10.3	44.1 ± 8.9	0.036
Cold ischemic time (min)	82.1 ± 45.5	73.7 ± 39.6	112.7 ± 48.9	0.0001
Warm ischemic time	43.0 ± 12.0	44.3 ± 12.4	37.8 ± 8.9	0.029
Arterial diameter	2.00 ± 0.76	1.94 ± 0.71	2.18 ± 0.89	0.198
Number of anastomosis				
Single	96 (88.1 %)	76 (89.4 %)	20 (83.3 %)	0.534
Double	12 (11.0 %)	8 (9.4 %)	4 (16.7 %)	
Triple	1 (0.9 %)	1 (1.2 %)		
Hepatic anastomosis time per anastomosis	45.2 ± 19.5	46.4 ± 20.7	38.7 ± 13.1	0.094
Hepatic artery thrombosis	0	0	0	
Hepatic artery stenosis				
Suspected mild stenosis by CT scan image within 12 months	39 (35.8 %)	28 (32.9 %)	11 (45.8 %)	0.245
Angiography performed	8 (7.3 %)	8 (9.4 %)	0	0.118
Angiography confirmed	6 (5.5 %)	6 (7.1 %)	0	0.181

Data are expressed as mean ± standard deviation. P values were calculated by Student's t test. *MELD* model for end-stage liver disease

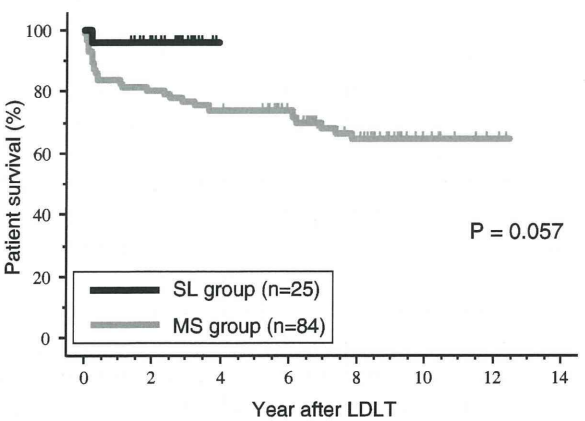

Fig. 1 Patient survival curves after LDLT. The patient survival in the surgical loupe (SL) group was better than that in the microscope (MS) group, although the difference didn't reach statistical significance ($P = 0.057$, log rank test). *Black line* SL group ($n = 25$), *Gray line* MS group ($n = 84$)

treatment. Two patients died after IVR, but in neither case was death related to the hepatic arterial complication; both died of bacterial/viral/fungal infections.

In contrast to the patients with DUS-based diagnosis of HAS ($n = 8$), including those with IVR-confirmed HAS ($n = 6$), the remaining patients (control group, $n = 101$) did not develop hepatic artery thrombosis and required no intervention for any hepatic arterial complications throughout the study period.

Risk factor analyses for HAS revealed only ABO incompatibility as being associated with a high risk of development of HAS ($P = 0.044$). None of the other factors, including arterial diameter and surgical method (microscope or surgical loupes) were found to be significant predictors of HAS (Table 2).

A comparative study of the MS and SL groups showed a tendency in the MS group toward higher frequency of use of right lobe grafts, a shorter cold ischemic time, and longer warm ischemic time, possibly due to its being a chronologically older series. In spite of the similar arterial diameter and number of anastomoses, the duration of performing each anastomosis tended to be shorter in the SL group (38.7 ± 13.1 min) than in the MS group (46.4 ± 20.7 min, $P = 0.094$). There was no patient among the study subjects

Table 2 Risk factor analyses for HAS

Clinical factors	*P* value	95 %CI
Surgical method		
Microscope versus surgical loupes	0.975	0.00 to >1000
Age, (years)	0.965	0.94 to 1.07
Gender (M/F)	0.328	0.07 to 2.39
PreOP MELD score	0.403	0.95 to 1.13
Donor age, (years)	0.085	0.82 to 1.01
Arterial diameter, (mm)	0.534	0.47 to 4.34
Anastomotic time, (min)	0.132	0.99 to 1.06
Graft weight/standard liver volume, (%)	0.472	0.00 to 213
Cold ischemia time, (min)	0.268	0.03 to 1.16
Warm ischemia time, (min)	0.416	0.97 to 1.09
Acute cellular rejection	0.983	0.00 to >1000
Graft type (left/right)	0.355	0.32 to 24.9

CI confidence interval, *MELD* model for end-stage liver disease

who developed hepatic artery thrombosis, and all of the 6 patients who developed HAS (5.5 %) confirmed by angiography belonged to the MS group.

Multidetector-row CT findings, which were categorized into three types (HAS, suspected/mild HAS, normal), were described for both IVR-confirmed HAS patients ($n = 3$) and the control group not fulfilling the DUS criteria for the diagnosis of HAS ($n = 57$) (Fig. 2). In most cases of IVR-confirmed HAS, the MDCT diagnosis was compatible with IVR-confirmed HAS, whereas a false positive MDCT diagnosis was obtained in a substantial number of cases of the control group. The false positive diagnosis rate of MDCT remained relatively high until 3 months after LDLT (100 % sensitivity and 72.8 % specificity at 3 months), but decreased thereafter until 12 months after LDLT (Fig. 2a, b).

The sensitivity, specificity, and accuracy of MDCT for the diagnosis of HAS are shown in Fig. 2c. The sensitivity was quite high throughout study period, whereas the specificity and accuracy were around 70 % until 6 months after LDLT, improving to over 90 % by 12 months after LDLT.

Discussion

In this study we investigated two different issues related to hepatic arterial anastomosis in LDLT. The first was to identify the risk factors for the development of hepatic arterial anastomotic complications, including a comparison of the surgical methods using either a microscope or surgical loupes for the arterial reconstruction. The second aim of the study was to evaluate the usefulness of MDCT in the diagnosis of hepatic arterial complications.

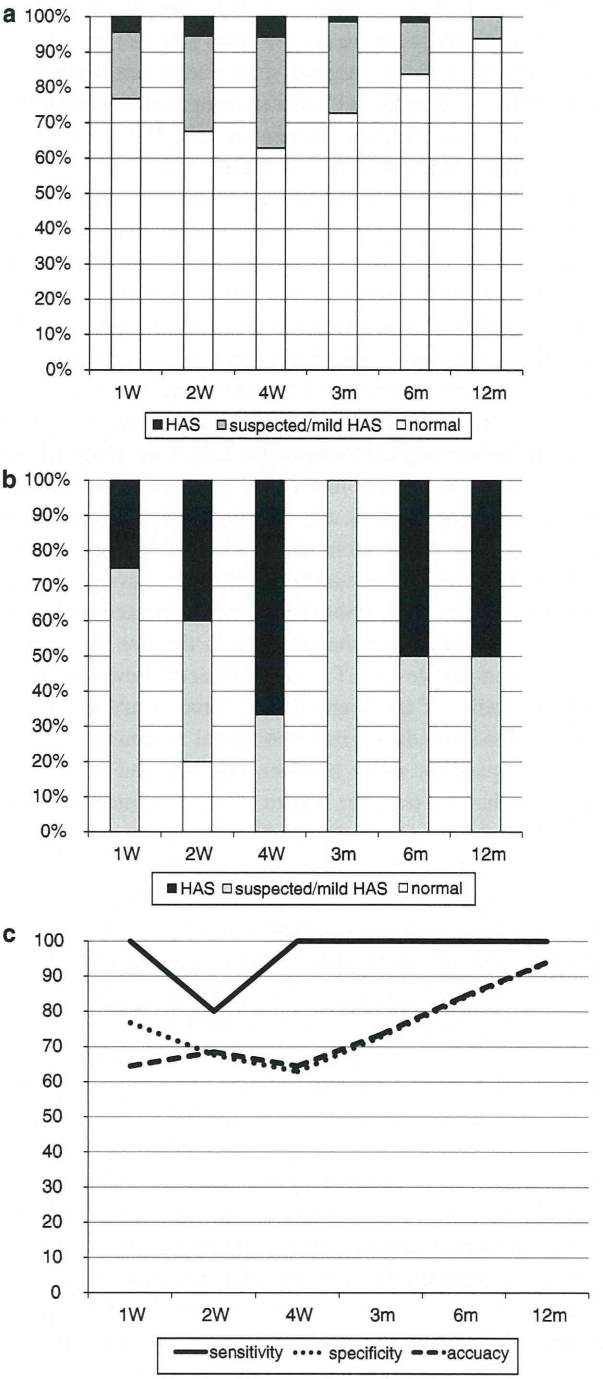

Fig. 2 HAS and MDCT diagnosis. **a** MDCT diagnosis of patients in the control group ($n = 57$), who did not fulfill the DUS-based criteria for the diagnosis of HAS. The false positive rate was relatively high until 3 months after LDLT (100 % sensitivity and 72.8 % specificity at 3 months), but it decreased thereafter up to 12 months after LDLT. **b** MDCT diagnosis in the IVR-confirmed HAS group ($n = 3$). **c** Sensitivity, specificity, and accuracy of MDCT in the diagnosis of HAS. The sensitivity was quite high throughout the study period, whereas the specificity and accuracy were around 70 % until 6 months after LDLT, improving to over 90 % by 12 months after LDLT

The risk factors for hepatic arterial complications after liver transplantation have not yet been clarified, except the anastomosis under a surgical microscope has been considered to be superior, with fewer complications, than that performed with surgical loupes in LDLT [8, 9]. Other studies have reported that continuous end-to-end suturing with a loupe yielded results equivalent to anastomosis under a microscope [23, 24]. In the present study, we found that ABO incompatibility was associated with a high risk of HAS, whereas none of the other factors examined, including the arterial diameter, history of acute cellular rejection, and the anastomosis method (microscope vs. surgical loupes) was found to be associated with the risk of development of HAS. Two (33.3 %) of the six recipients who underwent ABO-incompatible LDLT developed HAS ($P = 0.044$); therefore, this factor was considered a significant risk factor, although this interpretation should be validated with many more cases with ABO-incompatible LDLT. Both recipients survived, with an uneventful postoperative course and without antibody-mediated rejection. The reason underlying the increase in the risk of HAS in ABO-incompatible LDLT is not yet clear; however, there is a possibility of involvement of intimal injury associated with antibody-mediated immunological responses.

A comparative study between our MS and SL groups revealed that the time for hepatic arterial anastomosis was shorter in the SL group than in the MS group. The differences in the graft type, and in the warm and cold ischemic times between the two groups were considered to be mainly related to the chronological differences between the groups, and the influence of these parameters on the anastomosis time was considered to be negligible.

Similarly, the patient survival curve in the SL group was better than that in MS group, and that difference was also considered to be mainly related to the chronological differences between the groups. No case of IVR-confirmed HAS was encountered in the SL group, whereas HAS developed in six patients (7.1 %) in the MS group, although the difference did not reach statistical significance. These results show that the use of surgical loupes with a magnification power of 4.5× yielded at least similar outcomes for the anastomosis, and that the SL procedure was superior to the MS procedure in terms of the time required to perform the anastomosis. Setting up the device is much easier in the case of surgical loupes than in the case of a microscope. Surgical loupes (4.5×) can be safely substituted for a surgical microscope, but the choice should probably be left to the surgeon.

As for the second goal of our study, serial MDCT studies after LDLT showed that the sensitivity of this imaging modality for the detection of HAS was quite excellent within 12 months after LDLT, although the specificity was not optimal; up to 30 % false positive results were obtained, especially in the early post-transplant period (up to 3 months) after LDLT, whereas MDCT provided diagnosis with a rather high accuracy at 12 months after LDLT. In contrast, DUS-based criteria for HAS, namely, RI >0.6 combined with elevation of the serum AST/ALT, show 100 % sensitivity, 75 % specificity, and 93.6 % accuracy for the diagnosis of HAS during the first 12 months after LDLT. Furthermore, DUS was confirmed as being superior to MDCT for the diagnosis of HAS after LDLT.

Multidetector-row CT was also quite useful in detecting other arterial complications after LDLT [20, 21]. In contrast to a DUS study, MDCT can detect not only abnormalities in the hepatic artery but also abnormalities in other abdominal arteries, the portal vein, the hepatic vein, and the inferior vena cava. We found a superior mesenteric artery aneurysm and stenosis in two patients by MDCT, and both were successfully treated with antiplatelet agents. Blood flow to the liver graft can be evaluated easily by high-resolution MDCT. Therefore, it is worthwhile performing MDCT according to the follow-up schedule described in the present study. However, the rate of false positive diagnosis of HAS was relatively high during the first 3 months after LDLT, and this improved spontaneously over time. These data suggest that the abnormal findings on MDCT not supported by DUS-based criteria represent only a cautionary note for HAS, and that it may be sufficient to monitor the patient's course under therapy with antiplatelet agents, as long as the DUS-based criteria are not fulfilled.

In conclusion, our retrospective study revealed ABO-incompatible LDLT as a risk factor for HAS. Hepatic arterial anastomosis using surgical loupes tended to be time-saving and to yield similar or better results than traditional microscope anastomosis. Also, MDCT was a useful adjunct to a DUS study for the diagnosis of HAS; however, the substantially high rate of false positive diagnosis of HAS should be borne in mind in clinical practice.

Conflict of interest None declared

References

1. Sheiner PA, Varma CV, Guarrera JV et al (1997) Selective revascularization of hepatic artery thromboses after liver transplantation improves patient and graft survival. Transplantation 64:1295–1299
2. Millis JM, Cronin DC, Brady LM et al (2000) Primary living-donor liver transplantation at the University of Chicago: technical aspects of the first 104 recipients. Ann Surg 232:104–111
3. Ikegami T, Hashikura Y, Nakazawa Y et al (2006) Risk factors contributing to hepatic artery thrombosis following living-donor liver transplantation. J Hepatobiliary Pancreat Surg 13:105–109
4. Abbasoglu O, Levy MF, Vodapally MS et al (1997) Hepatic artery stenosis after liver transplantation—incidence, presentation, treatment, and long term outcome. Transplantation 63: 250–255

5. Kim SJ, Yoon YC, Park JH et al (2011) Hepatic artery reconstruction and successful management of its complications in living donor liver transplantation using a right lobe. Clin Transplant 25:929–938
6. Park YS, Kim KW, Lee SJ et al (2011) Hepatic arterial stenosis assessed with doppler US after liver transplantation: frequent false-positive diagnoses with tardus parvus waveform and value of adding optimal peak systolic velocity cutoff. Radiology 260:884–891
7. Sugawara Y, Tamura S, Kaneko J et al (2011) Single artery reconstruction in left liver transplantation. Surgery 149:841–845
8. Tanaka K, Uemoto S, Tokunaga Y et al (1993) Surgical techniques and innovations in living related liver transplantation. Ann Surg 217:82–91
9. Mori K, Nagata I, Yamagata S et al (1992) The introduction of microvascular surgery to hepatic artery reconstruction in living-donor liver transplantation—its surgical advantages compared with conventional procedures. Transplantation 54:263–268
10. Uchiyama H, Hashimoto K, Hiroshige S et al (2002) Hepatic artery reconstruction in living-donor liver transplantation: a review of its techniques and complications. Surgery 131:S200–S204
11. Wei WI, Lam LK, Ng RW et al (2004) Microvascular reconstruction of the hepatic artery in live donor liver transplantation: experience across a decade. Arch Surg 139:304–307
12. Ohdan H, Tashiro H, Ishiyama K et al (2007) Microsurgical hepatic artery reconstruction during living-donor liver transplantation by using head-mounted surgical binocular system. Transpl Int 20:970–973
13. Yang Y, Yan LN, Zhao JC et al (2010) Microsurgical reconstruction of hepatic artery in A–A LDLT: 124 consecutive cases without HAT. World J Gastroenterol 16:2682–2688
14. Li PC, Jeng LB, Yang HR et al (2012) Hepatic artery reconstruction in living donor liver transplantation: running suture under surgical loupes by cardiovascular surgeons in 180 recipients. Transplant Proc 44:448–450
15. Hedegard WC, Bhatt S, Saad W et al (2011) Hepatic arterial waveforms on early posttransplant Doppler ultrasound. Ultrasound Q 27:49–54
16. Sidhu PS, Ellis SM, Karani JB et al (2002) Hepatic artery stenosis following liver transplantation: significance of the tardus parvus waveform and the role of microbubble contrast media in the detection of a focal stenosis. Clin Radiol 57:789–799
17. Vit A, De Candia A, Como G et al (2003) Doppler evaluation of arterial complications of adult orthotopic liver transplantation. J Clin Ultrasound 31:339–345
18. Choi JY, Lee JY, Lee JM et al (2007) Routine intraoperative Doppler sonography in the evaluation of complications after living-related donor liver transplantation. J Clin Ultrasound 35:483–490
19. Garcia-Criado A, Gilabert R, Berzigotti A et al (2009) Doppler ultrasound findings in the hepatic artery shortly after liver transplantation. AJR Am J Roentgenol 193:128–135
20. Kim SY, Kim KW, Kim MJ et al (2007) Multidetector row CT of various hepatic artery complications after living donor liver transplantation. Abdom Imaging 32:635–643
21. Kayahan Ulu EM, Coskun M, Ozbek O et al (2007) Accuracy of multidetector computed tomographic angiography for detecting hepatic artery complications after liver transplantation. Transplant Proc 39:3239–3244
22. Vignali C, Bargellini I, Cioni R et al (2004) Diagnosis and treatment of hepatic artery stenosis after orthotopic liver transplantation. Transplant Proc 36:2771–2773
23. Tzeng YS, Hsieh CB, Chen SG (2011) Continuous versus interrupted suture for hepatic artery reconstruction using a loupe in living-donor liver transplantation. Ann Transplant 16:12–15
24. Enne M, Pacheco-Moreira L, Balbi E et al (2010) Hepatic artery reconstruction in pediatric living donor liver transplantation under 10 kg, without microscope use. Pediatr Transplant 14: 48–51

Cancer Chemother Pharmacol (2013) 72:1325–1333
DOI 10.1007/s00280-013-2311-x

ORIGINAL ARTICLE

Evaluation of safety parameters and changes in serum concentration in liver transplant recipients treated with doxorubicin during the anhepatic period

Shogo Kobayashi · Hiroshi Wada · Naoki Hama · Hirofumi Akita · Koichi Kawamoto · Hidetoshi Eguchi · Koji Umeshita · Yuichiro Doki · Masaki Mori · Hiroaki Nagano

Received: 8 May 2013 / Accepted: 25 September 2013 / Published online: 13 October 2013

Abstract
Purpose Because of the recurrence of hepatocellular carcinoma (HCC) at the graft after liver transplantation, circulating HCC cells may be present during the anhepatic period. Intravenous doxorubicin (DOX) is used during the anhepatic period to combat these cells; however, pharmacokinetics data have been poorly analyzed. This study aims to investigate DOX administration during the anhepatic period.
Patients and methods We administered 5 mg/m^2 DOX immediately after liver removal and compared serum DOX concentrations at several intervals during the anhepatic period in patients who underwent liver transplantation because of liver cirrhosis and HCC ($n = 3$) and patients who underwent liver resection owing to HCC with portal vein tumor thrombi ($n = 5$). We also measured serum DOX concentrations and pharmacokinetic parameters in transplant patients that received 3–15 mg/m^2 DOX ($n = 3$ per dose level). We evaluated transplant patients' adverse drug reactions and survival.
Results At 10 and 30 min after DOX administration, serum DOX concentrations were elevated two- to threefold in transplant patients versus resection patients. Dose escalation in transplant patients exhibited a prolonged $T_{1/2}$ in the one-compartment model and $T_{1/2}$ β in the two-compartment model, as well as a dose-dependent elevation of the area under the curve. No obvious adverse drug reactions were noted at 3–15 mg/m^2 DOX. In transplant patients, 5-year recurrence-free survival was 68.8 %; overall survival was 100.0 %.
Conclusion During the anhepatic period, serum DOX concentrations were elevated two- to threefold, $T_{1/2}$ was prolonged dose dependently, and up to 15 mg/m^2 DOX could be safely administered.

Keywords Liver transplantation · Hepatocellular carcinoma · Doxorubicin · Pharmacokinetics · Anhepatic period

S. Kobayashi · H. Wada · N. Hama · H. Akita · K. Kawamoto · H. Eguchi · K. Umeshita · Y. Doki · M. Mori · H. Nagano (✉)
Department of Surgery, Osaka University, Suita, Osaka 565-0871, Japan
e-mail: hnagano@gesurg.med.osaka-u.ac.jp

Introduction

Viral hepatitis and cirrhotic liver are major risk factors associated with hepatocellular carcinoma (HCC) [1, 2]. Because these are chronic conditions that also affect liver function, and some cases of HCC are contraindicated for surgical resection because of poor liver function. In these cases, liver transplantation is becoming an alternative strategy to combat this tumor, even in patients with Child-Pugh C liver function [3, 4]. Although Milan and other criteria [4–6] have proposed indications for liver transplantation due to HCC with cirrhotic liver, the prognosis in patients with HCC exceeding these criteria is quite poor [5–8]. Accordingly, several authors have tried neo-adjuvant therapy for down-staging, as well as intra-operative and post-operative adjuvant chemotherapy [4, 9, 10]. Because of HCC recurrences at the liver graft after transplantation, some authors have suggested that circulating HCC cells may be present during the anhepatic period [11–14]. Adjuvant chemotherapies have been tried against these small clusters of HCC cells [15].

Doxorubicin (DOX) is one of the major drugs employed against HCC in several situations, both for unresectable HCC and in an adjuvant setting. For example, several clinicians have performed adjuvant chemotherapy with DOX

after the resection of HCC with portal vein tumor thrombus (PVTT) [16, 17]. In liver transplantation, several clinicians have tried chemotherapy during the anhepatic period [18, 19] or adjuvant chemotherapy with DOX [9, 20] in patients with HCC exceeding Milan criteria.

However, pharmacological analysis of DOX during the anhepatic period and after reperfusion during liver transplantation is rarely investigated. This drug is mainly metabolized in the liver, and the serum concentration would reportedly remain high in patients with liver dysfunction [21–24]. In dogs, serum DOX concentration was measured during the anhepatic period and exhibited only a 50 % reduction in total body clearance [25, 26]. In the present study, we measured serum DOX concentration during the anhepatic period in the transplant recipients. We also compared these results to serum DOX concentrations in patients who underwent liver resection. Furthermore, we evaluated safety by performing a detailed investigation of the adverse events and adverse drug reactions in these series.

Patients and methods

Patients

Between 2003 and 2011, we measured serum DOX concentration in 12 patients who underwent liver transplantation because of liver cirrhosis and HCC (TSPL group). We also measured serum DOX concentration in five patients who underwent liver resection and PVTT removal owing to HCC with PVTT (RESC group). The first three patients in the TSPL group were treated with 5 mg/m^2 DOX, and we compared pharmacokinetic data from the TSPL group with data from the RESC group. Previous data [25, 26] indicated that DOX clearance would be reduced by 50 %; therefore, for safety reasons, we administered 5 mg/m^2 DOX (the common dose for systemic administration in the context of HCC is 45–75 mg/m^2 [27–29]) and compared the pharmacokinetic data of the TSPL and RESC groups. After pharmacokinetic data were confirmed in the TSPL group at 5 mg/m^2 DOX, we administered DOX at several dose levels (3, 10, and 15 mg/m^2), calculated pharmacokinetic data, and evaluated adverse events at each dose level. Patients' characteristics were prospectively collected. All patients underwent surgery at our institution. The protocol was approved by the institutional review board at our hospital, and written informed consent was obtained from each patient.

DOX administration, sample collection, and measurement DOX concentration

The time course of DOX administration and sample collection is depicted in Fig. 1a. In the TSPL group, patients underwent liver transplantation because of liver cirrhosis with HCC. At 5 min after explantation of the cirrhotic liver, 3–15 mg/m^2 of DOX were administered intravenously. Five milliliter peripheral blood samples were obtained at 0, 10, 30, 60, and 120 min after DOX administration until reperfusion. We also collected blood samples at 0, 10, 30, and 60 min post-reperfusion. The RESC group underwent liver resection with the removal of PVTT. We administered 5 mg/m^2 DOX to each RESC patient 5 min after the liver resection was completed. Blood samples were obtained at 0, 10, 30, 60, and 120 min after DOX administration.

All blood samples were stored at 4 °C, centrifuged at 3,000 rpm for 10 min, and frozen at −80 °C before the DOX concentrations were measured. Serum DOX concentrations were measured by high-pressure liquid chromatography at Kyowa Hakko Kogyo Co., Ltd., Japan. The serum concentration curves, pharmacokinetic parameters, and area under the DOX concentration curve from 0 to 120 min (AUC_{120}) were determined for each patient. Various parameters were calculated using the one- or two-compartment infusion model ($C(t) = Ae - \alpha t$ for the one-compartment model and $C(t) = Ae - \alpha t + Be - \beta t$ for the two-compartment model) and LAB Fit Curve Fitting Software 7.2.41 (Wilton and Cleide Pereira da Silva, Brazil). AUC_{120} was calculated using the trapezoidal model.

Evaluation of adverse events and adverse drug reactions

We evaluated adverse events and adverse drug reactions according to CTACE version 4.0, retrospectively, during the first 7 days after the surgery. For adverse drug reactions, we considered events that were unrelated to liver transplantation and the use of immunosuppressant medications.

Statistical analysis

Data were expressed as mean ± standard error. Differences between groups were tested using Student's t test and the chi-squared test, and differences were considered statistically significant at $p < 0.05$. All statistical analyses were performed using StatView J-5.0 software (SAS, Cary, NC).

Results

Comparison of pharmacokinetic parameters between TSPL and RESC groups at 5 mg/m^2 DOX

We summarized these patients' characteristics in Table 1. Major characteristics (e.g., age, sex, body height and weight, and ratio of hepatitis) were similar between the groups. Characteristics specific to liver function were expected to be worse in the TSPL group than in the RESC