Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging-guided risk assessment in living donor liver transplant patients with postoperative complications: a pilot study

M. KOLU[1], A.S. KAHRAMAN[2], S. AKBULUT[3], I.O. YILDIRIM[2]

[1]Department of Radiology, Harran University Faculty of Medicine, Sanliurfa, Turkey
[2]Department of Radiology, Inonu University Faculty of Medicine, Malatya, Turkey
[3]Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Turkey

Abstract. – OBJECTIVE: To evaluate whether gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) enhanced magnetic resonance imaging (MRI), the measurements of quantitative and qualitative parameters on hepatobiliary phase images can predict the risk of postoperative complications in patients underwent living donor liver transplantation (LDLT)

PATIENTS AND METHODS: We obtained Gd-EOB-DTPA-enhanced 3 Tesla MRI before living donor hepatectomy in donors (donor group; n=30) and after LDLT in their recipients (recipient group; n=30). MRIs were evaluated in terms of quantitative and qualitative variables. Quantitative parameters included relative liver enhancement value, biliary signal intensity value, and muscle signal index value. Qualitative parameters included visual evaluation of the liver and biliary enhancement on hepatobiliary phase images. Patients were followed up for postoperative biliary and vascular complications and divided according to the presence and absence of complications. The relationship between MRI parameters and postoperative complications was statistically analyzed.

RESULTS: The mean relative liver enhancement values, mean biliary signal values, and muscle signal index were significantly lower in recipients with postoperative complications than those in donors and recipients without complications ($p < 0.001$). Visual assessments of liver enhancement and biliary signal were also significantly different in recipients with postoperative complications than that in donors and recipients without complications ($p < 0.001$).

CONCLUSIONS: Quantitative and qualitative MRI parameters obtained by Gd-EOB-DTPA-enhanced MRI on hepatobiliary phase images may potentially become a reliable tool for the assessment of the risk for postoperative complications after LDLT.

Key Words:
Living donor liver transplantation, Postoperative complications, Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid, Magnetic resonance imaging.

Introduction

Since first liver transplantation (LT) was performed by Starzl and colleagues in 1963[1], LT became the gold standard therapy for patients with many liver disease, including end stage chronic liver disease, primary or metastatic liver cancer, metabolic liver diseases and acute liver failure[1]. Living donor liver transplantation (LDLT) is an effective treatment choice, especially in areas where deceased grafts are in short supply[1-3]. LT can be accompanied by various complications, including vascular (stenosis or thrombosis of the hepatic artery, portal, hepatic, or inferior cava vein), biliary (stenosis, bile leaks, bilioma), and other clinical complications (abscess, hematoma, neoplasm, cirrhosis, rejection). Therefore, liver transplant recipients are closely followed postoperatively to examine complications closely related with liver function.

Several studies[4-6] have been conducted to evaluate the graft function after LT and attempt to predict the survey. On the other hand, indocyanine green retention, Child-Pugh classification

Corresponding Author: Mehmet Kolu, MD; e-mail: drrdylg@gmail.com

and MELD scoring are the most commonly accepted methods to evaluate liver function in patients with end stage liver disease[7-9]. Many studies[10-12] showed that none of these parameters sufficiently predicted liver failure. Magnetic resonance imaging (MRI) has been proven as a valuable tool to detect vascular and biliary complications[3]. To determine the risk of liver failure and be aware of its functional reserve, many recent studies have been conducted on liver MRI obtained by gadoxic acid[13-16]. We aimed to investigate whether gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI with quantitative and qualitative parameter measurements on hepatobiliary phase images can predict the risk of postoperative complications in patients underwent LDLT.

Patients and Methods

Patients Selection

Between August 2016 and July 2017, 35 living liver donor (LLD) and their 35 recipients were prospectively assessed for this study in Inonu University Liver Transplant Institute, Malatya, Turkey. This study was performed in one single center and approved by the institutional Ethics Board. Although LLDs were evaluated before LDLT, 5 pairs of donor-recipient participants were excluded from the study due to the lack of dynamic-enhanced MR images of recipients after the LT for the following reasons: three recipients died and two underwent re-transplantation. Hence, 30 LLDs (18 men and 12 women, with mean age of 26 years) and 30 recipients (22 men and 8 women, with mean age of 51.5 years) who underwent Gd-EOB-DTPA-enhanced dynamic MRI were included. MRI examinations were performed 1-7 days before LDLT in LLD candidates (n=30) and their recipients (n=11) and 10-15 days after LDLT in recipients (n=30). Preoperative Gd-EOB-DTPA-enhanced dynamic MRI could not be performed on 19 of 30 recipients included in the study for various reasons. Therefore, only 11 recipient's MRI images were used for preoperative comparison.

Various causes of liver disease were identified in patients. Chronic viral hepatitis (hepatitis B virus [n = 12], hepatitis C virus [n = 2]), chronic viral hepatitis B and HCC (n = 7), and chronic viral hepatitis B plus D virus (n = 2) were the predominant causative factors, accounting for >74% of patients admitted with liver disease. Miscellaneous causes included Budd-Chiari syndrome (n = 2), Wilson disease (n = 1), and Cryptogenic cirrhosis (n = 4).

Magnetic Resonance Imaging (MRI)

Technical Features of MRI

All patients underwent MRI using a 3-T scanner (Magnetom Skyra, Version E11: Siemens Healthcare, Erlangen, Germany) with receiver channels, using one 18-channel phased-array body coil anteriorly and one 32-channel spine cluster posteriorly. Contrast-enhanced sequences consisted of 1+4 phases of axial three-dimensional breath-hold, T1-weighted, gradient-echo sequences, known as volumetric interpolated breath-hold examination. Axial dynamic images were acquired using a bolus-tracking system, immediately (arterial phase), and at 70 s (portal venous phase), at 4 min (transitional phase), and 20 min (Hepatobilier phase) after a contrast injection. In addition, a coronal 3D breath-hold T1-weighted, gradient-echo sequence was obtained in the hepatobiliary phase. The MRI examination protocol also included axial in- and opposed-phase T1-weighted images, conventional T2-weighted MR cholangiopancreatography, and diffusion-weighted images. A total of 0.025 mmol/kg for Gd-EOB-DTPA (Primovist, Bayer Schering Pharma, Berlin, Germany) was injected through the antecubital vein using a power injector at a 2 ml/s rate, followed by 20 ml of physiological saline. All Gd-EOB-DTPA-enhanced dynamic MRI were prospectively evaluated by two radiologists with at least 10 years and 3 years of experience with regard to liver imaging, using a Sectra PACS (Picture Archiving and Communication Systems) workstation. Images were analyzed throughout the daily interpretation of liver images.

Quantitative Assessment of MRI

Quantitative relative liver enhancement (RLE) values were calculated as the ratio of mean signal intensity (SI) between pre-contrast and 20-min images after obtaining the mean value of four regions of interest (ROIs ≅ 1.5-2 cm^2) taken from the liver parenchyma with exclusion of major vascular structure branches and artifacts in the lateral segment affected by cardiac motion (Figure 1A).

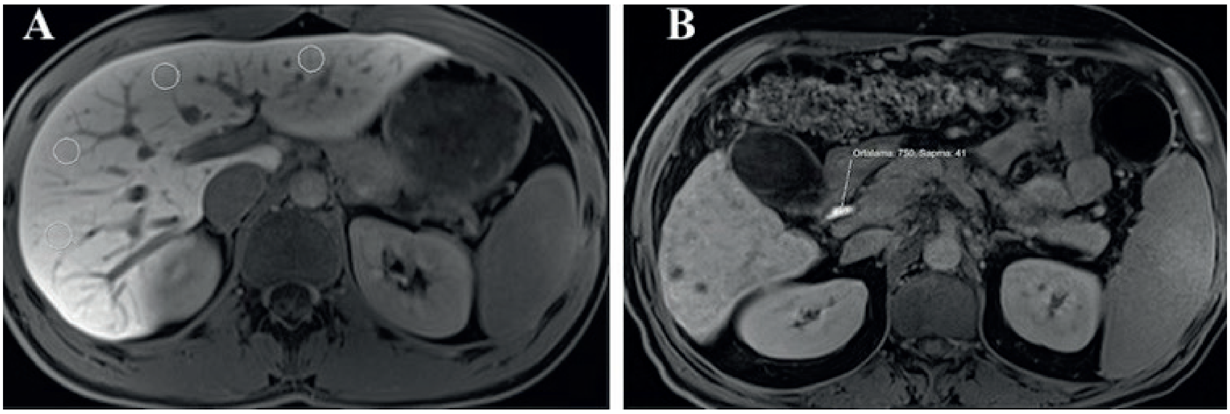

Figure 1. A, Quantitative RLE values were calculated as the ratio of the mean SI between precontrast and 20-min images after obtaining the mean value of four regions of interest (ROIs ≅ 1.5-2 cm^2) taken in the liver parenchyma with exclusion of major branches of vascular structures and artifacts in the lateral segment affected by cardiac motion. **B,** Biliary SI was calculated with ROI placement into the common bile duct.

$$\text{RLE} = \frac{\text{HBP-enhanced SI liver-unenhances SI liver}}{\text{Unenhanced SI liver}} \times 100$$

Biliary signal intensity (BSI) was calculated by placing an ROI at the common bile duct during the hepatobiliary phase (Figure 1B). Muscle signal index (MSI) was taken as the mean value of 4 ROIs, comprising two ROIs in the right erector spine muscle and two ROI in the left, with exclusion of ambient fat and artifacts. Muscle signal index values were calculated during the hepatobiliary phase using the following definition:

$$\text{MSI} = \frac{\text{Signal intensity of liver parenchyma}}{\text{Signal intensity of muscle}} \times 100$$

Qualitative Assessment of MRI

The main branches of intrahepatic and extrahepatic biliary trees were qualitatively evaluated during the hepatobiliary phase. The visibility of these biliary structures was graded according to contrast medium enhancement of biliary structures (score 0: absent contrast media; score 1: present only in intrahepatic branches; score 2: present in both intrahepatic and extrahepatic branches and duodenum)[17]. Liver signal intensity (LSI) was visually assessed and graded according to liver enhancement in comparison with portal vein signal intensity (score 1: the LSI definitely higher than the portal vein signal; score 2: the LSI slightly higher than the portal vein signal; score 3: the LSI almost equal to the portal vein signal; and score 4: the LSI lower than the portal vein signal).

Statistical Analysis

Statistical analysis was performed using the IBM SPSS (Statistical Package for Social Sciences; IBM Corp., Armonk, NY, USA) software version 22.0. Distributions were analyzed to test the normality using the Shapiro-Wilk test. Data were presented as median values (min-max), mean values (SD), and number (percentage). Pearson's chi-squared test was used to compare qualitative variables. Kruskal-Wallis test was used to compare quantitative variables and when significant differences were found, stepwise step-down multiple comparisons were carried out using Kruskal Wallis 1-way analysis. *p*-values of <0.05 were considered to indicate statistical significance.

Results

Early postoperative complications (15–20 days postoperatively) included stenosis of the biliary anastomosis and biliary leak (n = 12), steanosis of the portal vein anastomosis (n = 3), steatosis of the hepatic artery anastomosis (n = 1), thrombosis of the reconstructed graft hepatic veins (Seg V and VIII) (n = 10), urinary tract infection (n = 2), intra-abdominal abscess (n = 2), and pneumonia (n = 1). Some patients had more than one complication. A total of 20 recipients have experienced at least one complication, and 10 had no complications.

Finally, all participants were grouped as follows: Group I donors (n = 30), Group II preoperative patients with liver disease (n = 11), Group III postoperative patients with complications (n =

20), and Group IV postoperative patients without complications (n = 10). Results of comparing the mean RLE, BSI, and MSI among all groups. The median RLE, BSI, and MSI values were significantly lower in groups II and III than that in groups I and IV. Statistically significant difference was found for the median RLE and BSI between groups I and IV. No statistically significant difference was found for the MSI between groups 1 and IV. Details on statistical analysis are given in Table I. Subgroup analyzes are also given below the Table I.

Results of comparing the visual liver enhancement relative to portal vein scores among all groups. For all groups, visual liver enhancement relative to the portal vein scores was significantly lower in donor candidates (all have score 1) than that in other groups. The highest liver scores to the portal vein enhancement ratio were observed in patients with liver disease before transplantation. Second, patients with complication after the transplantation showed high liver scores to portal vein enhancement ratio (Table II).

The results of comparing the visual biliary excretion scores among all groups. For all groups, visual biliary excretion scores were significantly higher in donor candidates (all have score 2) than that in other groups. The lowest scores of biliary excretions were observed in patients with liver disease before transplantation and patients with complication after the transplantation. In patients without complication after the transplantation, 80% of population demonstrated best biliary excretion scores, whereas none of them had scores of 0 (Table III).

Discussion

Based on our literature reviews, this is the first study evaluating the qualitative and quantitative MRI parameters on hepatobiliary phase images in LDLT recipients and comparing these parameters between patients with and without complications. Therefore, this study compared the quantitative and qualitative MRI parameters between donors and recipients before and after LT. Due to the lack of standardization in quantitative and qualitative MRI parameters, quantitative values and qualitative scores in the graft liver were compared with their own donors.

In LDLT, graft liver function decreased after the transplantation and hepatobiliary phase images can usefully demonstrate this decrease. The mean RLE, MSI, and biliary SI values in patients without postoperative complications were comparable with that in donors, indicating that liver transplant recipients without postoperative complications do not have an inferior hepatic uptake and biliary excretion of gadoxetic acid after 20 min of injection, as we observed as a general trend for these values to be slightly inferior, but in part equal to the donors.

Liver and biliary enhancement should be determined to estimate liver function[18]. Many studies[19-21] suggested that gadoxic acid causes decreased hepatocyte involvement in liver dysfunction, such as cirrhosis. The evaluation of liver enhancement was also found useful to predict early complications after LDLT. Liver and biliary enhancement at 20-min image after the Gd-EOB-DTPA injection had significant differences between donors and patients with postoperative complications after the transplantation. This means the liver and biliary enhancement may be closely correlated with postoperative complications.

We assume that Gd-EOB-DTPA-enhanced MRI could be used as an adjunct tool to estimate the occurrence of postoperative complications. Patients with complications after the transplantation had a statistically significantly lower RLE values than those without complications.

Table I. The comparison of parameters including RLE, biliary signal intensity and muscle signal index.

	Preop donor (n = 30) (Group I)	Preop recipient (n = 11) (Group II)	Recipient with postop complication (n = 20) (Group III)	Recipient without postop complication (n = 10) (Group IV)	*p*
RLE	102 (57-151)[e,f]	40 (20-78)[d,e]	54 (22-111)[d,f]	75 (29-141)	< 0.001
BSI	690 (350-1190)[g,h]	350 (100-1150)[h]	207 (125-630)[g]	480 (135-1100)	< 0.001
MSI	2.5 (2.0-3.3)[b,c]	1.6 (0.6-2.2)[a,b]	1.9 (1.1-2.9)[c]	2.4 (1.5-3.1)[a]	< 0.001

[a](p=0.008), [b](p<0.001), [c](p=0.001), [d](p=0.44), [e](p<0.001), [f](p <0.001) [g](p <0.001), [h](p =0.007) RLE: Relative liver enhancement, MSI: Muscle Signal intensity, Variables expressed as median (min-max).

Table II. The visual evaluation of liver enhancement relative to portal vein (Score = Liver enhancement visual scoring).

	Preop donor (n = 30) (Group I)	Preop recipient (n = 11) (Group II)	Recipient with postop complication (n = 20) (Group III)	Recipient without postop complication (n = 10) (Group IV)	p
1	30 (100)[a]	0 (0)[b]	3 (15)[b,c]	6 (60)[a,c]	< 0.001
2	0 (0)[a]	5 (45.5)[b]	13 (65)[b]	3 (30)[b]	
3	0 (0)[a]	3 (27.3)[b]	4 (20)[a,b]	1 (10)[a,b]	
4	0 (0)[a]	3 (27.3)[b]	0 (0)[a,b]	0 (0)[a,b]	

*Different letters at the same row demonstrate statistical significancy.

Significant differences in RLE and mean biliary SI values were observed between the patient donors and without postoperative complications. In contrast, no significant difference was found among these groups in MSI values. Considering that RLE and mean biliary SI values provide valuable information about the liver function, more sensitive statistical results on MSI values suggest that it may be a more valuable parameter to determine the functional liver reserve.

In this study, a visual assessment of biliary excretion and liver enhancement was performed during hepatobiliary phase images, and qualitative parameters were obtained. Tschirch et al[22] revealed the satisfactory visualization of the biliary system in only 40% of patients with liver disease after the Gd-EOB-DTPA injection. In normal individuals, 50% of gadoxetic acid is absorbed into the hepatocyte by means of organic anionic transporters (OATPs) in the hepatocyte membrane and then excreted into the bile canaliculi by means of a multi-drug resistance (MRGP2) protein[23,24]. In this respect, we thought that biliary signal and liver enhancement measurement might provide information about the absorption and excretion of gadoxetic acid in the liver. We investigated that slightly more than half of patients with liver disease showed adequate visualization of the biliary system. In this study, the ratio of sufficient visualization of biliary branches in patients with postoperative complications was 50%, which was definitely lower than that in the donors (100%) and patients without postoperative complications (80%). Our results showed that 15% of recipients with postoperative complications showed no biliary enhancement, and none of the recipients without postoperative complications showed no biliary enhancement after the Gd-EOB-DTPA injection. Additionally, visual liver enhancement rates of patients with postoperative complications in this study were significantly lower (85%) compared to donors (0%) and patients without postoperative complications (40%). We believe that the evaluation of qualitative biliary and liver enhancement may be used as a noninvasive prognostic biomarker for the occurrence of complications after LDLT.

Limitations

This study is strengthened by statistically determining and being prospective. Nevertheless, one of the limitations of this study is the limited number of participants studied. Second, time interval between the operation and MRI examination is 10-15 days, which may not be sufficient to optimally evaluate all qualitative and quantitative parameters. Conversely, we believe that approximately 80% of regeneration completed at this time interval and have been presently optimized[25]. Finally, quantitative measurements are known to be subject for inter- and intra-observer variability; therefore, we measured four ROIs and only recorded the median values.

Table III. The visuality of contrast media in biliary tree (Score= Biliary excretion visual scoring).

	Preop donor (n = 30) (Group I)	Preop recipient (n = 11) (Group II)	Recipient with postop complication (n = 20) (Group III)	Recipient without postop complication (n = 10) (Group IV)	p
0	0 (0)[a]	3 (27.3)[b]	3 (15)[a,b]	0 (0)[a,b]	< 0.001
1	0 (0)[a]	1 (9.1)[a,b]	7 (35)[a,b]	2 (20)[a,b]	
2	30 (100)[a]	7 (63.6)[b]	10 (50)[a,b]	8 (80)[a,b]	

Conclusions

Our study demonstrates that quantitative and qualitative MRI parameters obtained by Gd-EOB-DTPA-enhanced MRI on hepatobiliary phase images can help assess the risk for postoperative complications in patients underwent LDLT. Further longitudinal studies are needed to investigate the relationship between quantitative and qualitative MRI findings obtained on Gd-EOB-DTPA-enhanced MRI and postoperative complications after LDLT, as well as to explore the ability of this noninvasive technique to estimate the exact risk for postoperative complications.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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