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Half-dose gadoxetic acid-enhanced liver magnetic resonance imaging in patients at risk for nephrogenic systemic fibrosis

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ABSTRACT

Purpose: To evaluate the feasibility of half-dose gadoxetic acid (0.0125 mmol/kg) for liver MRI at 3-T compared to standard-dose (0.025 mmol/kg) in patients at risk for nephrogenic systemic fibrosis (NSF).
Materials and methods: Forty patients who underwent both half-dose and standard-dose gadoxetic acid-enhanced MRIs were included. Contrast enhancement index (CEI) was calculated for liver, aorta, pancreas and kidney. Two observers independently rated and performed a one-to-one direct comparison of enhancement quality for both groups.
Results: Liver CEIs were not significantly different on arterial phase between the two groups but CEIs of standard-dose MRIs were greater than half-dose MRIs on other phases ($P < 0.001$). CEIs were not significantly different on arterial phase for the aorta or on any phases for the pancreas. Kidney CEIs of standard-dose MRIs were greater than half-dose MRIs on all phases ($P < 0.05$). Enhancement quality of both groups was diagnostic and did not significantly differ for any organs. In one-to-one direct comparisons of enhancement quality, equal ratings were given in 87.5% (35/40) of cases by observer 1 and 85.0% (34/40) by observer 2.
Conclusion: Liver MRI using half-dose gadoxetic acid at 3-T can be a feasible alternative for standard-dose MRI in patients at risk for NSF.

1. Introduction

Gadolinium-based contrast agents (Gd-CAs) have become the most commonly used contrast agents for magnetic resonance imaging (MRI) since they were first used in humans in 1980s [1]. Gd-CAs have generally been considered safe. However, a strong association between use of Gd-CAs in patients with renal disease and nephrogenic systemic fibrosis (NSF), a debilitating disease causing fibrosis of the skin and inner organs first reported in 2000 [2], has been observed [3–7]. As a result, several medical societies released guidelines restricting Gd-CA use [8]. The guidelines generally recommend that alternative diagnostic examinations that do not use a Gd-CA should be considered for patients at risk for NSF. If the potential benefits of a Gd-CA-enhanced MRI outweigh the risk of NSF, the lowest possible dose of Gd-CA required for diagnostic image quality should be used.

Gadoxetic acid is a gadolinium-based hepatocyte-specific T1 contrast agent that has only recently appeared on the market. Therefore, data are limited on the association between gadoxetic acid and NSF. Although no uncompounded cases have been reported, gadoxetic acid also is a potential risk factor for NSF development. Gadoxetic acid is classified in the intermediate-risk group for NSF by the European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) (http://www.esmrmb.org), and in the medium-risk group by the European Medicines Agency (EMEA) (http://www.ema.europa.eu). Therefore, the lowest possible dose of gadoxetic acid that is necessary should be used in patients at risk for NSF. De Campos et al. [9] evaluated the feasibility of reduced doses of gadobenate dimeglumine for abdominal MRI at 3-T and reported that a low dose could be used for abdominal MRI in patients with poor renal function. However, to the best of

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Table 1
Basic characteristics of patients.

	At the time of half dose-MRI	At the time of standard dose-MRI	*P*-value
Median study interval (days) median (range)	105 (55–156)		
Age (years)	66.4 ± 8.0		
Sex (women/men)	8/32		
AST (U/l)	35.7 ± 21.2	35.2 ± 24.7	0.836
ALT (U/l)	29.3 ± 18.2	30.6 ± 25.2	0.550
Albumin (g/dl)	4.3 ± 0.4	4.3 ± 0.4	0.368
Total bilirubin (mg/dl)	0.9 ± 0.5	0.8 ± 0.4	0.297
INR	1.1 ± 0.2	1.1 ± 0.1	0.449
Child–Pugh score (5/6/7)	36/4/0	36/3/1	0.655
Estimated GFR (ml/min)	46.7 ± 13.1 (4.8–58.5)	66.0 ± 4.14 (60.4–80.1)	<0.001

Note: AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; GFR, glomerular filtration rate. Data are mean ± standard deviation. Values in parentheses are ranges.

our knowledge, no studies have reported the feasibility of reduced doses of gadoxetic acid for abdominal MRI in patients at risk for NSF. Therefore, the purpose of our study was to evaluate the feasibility of half-dose gadoxetic acid (0.0125 mmol/kg) for liver 3-T MRI compared with the standard dose (0.025 mmol/kg) in patients at risk for NSF.

2. Materials and methods

This retrospective study was approved by our Institutional Review Board and informed consent was waived.

2.1. Patients

Between August 2011 and August 2013, 45 patients underwent liver MRI using both half-dose gadoxetic acid (0.0125 mmol/kg) and standard-dose (0.025 mmol/kg) within a 6-month interval. Five patients were excluded because of severe motion artifacts ($n = 3$) or inadequate timing of arterial phases ($n = 2$), so no precise hepatic arterial dominant phase was acquired for both standard-dose and half-dose MRIs. Hepatic arterial dominant phase was defined as the presence of contrast in the hepatic arteries and in the portal veins, and the absence of contrast in the hepatic veins [10]. Thus, 40 patients constituted the final study group. The reasons for liver MRI were: follow-up after treatment of hepatocellular carcinomas (HCCs) ($n = 37$), HCC screening ($n = 2$) and workup for hepatic metastasis after operation for ampulla of Vater cancer ($n = 1$). The basic characteristics of included patients are in Table 1.

At our institution, all patients with renal disease or suspected renal problems routinely have estimated glomerular filtration rate (eGFR) checked within a week of gadoxetic acid-enhanced liver MRI. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation. In our institution, guidelines for the use of gadoxetic acid in patients with renal disease were established based on the 2010 American College of Radiology (ACR) recommendations for Gd-CA use [11,12]. Our institution guidelines are that for patients with chronic kidney disease (CKD) stage 3B or higher (eGFR $\leq$44 ml/min/1.73 m^2) [13], routine MRI sequences except enhancement studies are obtained and images are reviewed by a radiologist. After then, if enhancement study is essential for evaluation of liver lesions, the use of half-dose gadoxetic acid is considered. In patients with CKD stage 3A (eGFR 45–59 ml/min/1.73 m^2), the use of a half dose is considered. In patients with CKD stage 2 or lower (eGFR $\geq$ 60 ml/min/1.73 m^2), a standard dose of gadoxetic acid is used.

2.2. MRI technique

All MRIs used a 3-T whole-body MRI system (Intera Achieva 3-T, Philips Healthcare, Best, the Netherlands) with a 16-channel phased-array receiver coil. For gadoxetic acid-enhanced imaging (Primovist; Bayer Schering Pharma, Berlin, Germany), unenhanced, arterial-phase, portal-phase, delayed, and 20-min hepatobiliary phases were obtained using a T1-weighted 3D turbo-field-echo sequence (T1 high-resolution isotropic volume examination, THRIVE, Philips Healthcare) after intravenous administration of contrast agent. Time for arterial phase imaging was determined using the MRI fluoroscopic bolus detection technique. The bolus of injected contrast agent arrives in the descending aorta at 15–30 s after contrast injection. The arterial phase is obtained at about 5 s after the bolus arrival in the descending aorta. Portal phase, delayed phase and hepatobiliary phase were obtained at 60 s, 3 min and 20 min after contrast injection. Using a power injector, contrast agent was administered intravenously at 2 ml/s for a half dose of 0.0125 mmol/kg body weight and a standard dose of 0.025 mmol/kg body weight, followed by a 20 ml saline flush. The scanning parameters were as follows: TR/TE, 3.1/1.5; flip angle, 10°; matrix size, 256 × 256; bandwidth, 995.7 Hz/pixel; section thickness, 2 mm; field of view, 32–38 cm; acquisition time, 16.6 s; number of excitations, 1.

2.3. Quantitative analysis

Gadoxetic acid is usually used for liver imaging and in our study, all included patients underwent gadoxetic acid-enhanced MRI for evaluation of liver lesions. Therefore, enhancement of the liver was primarily assessed. However, in clinical practice, evaluation of other upper abdominal organs that are covered on liver MRI also occurs. For this reason, aorta, pancreas and kidney were also evaluated. Degree of enhancement of the liver, aorta, pancreas and renal cortex was determined by measuring signal intensity (SI) using operator-defined region-of-interest (ROI) (1–2 cm^2). ROIs covered the same anatomic location on all images in each patient. Areas of focal changes in SI due to previous treatment for HCC, large vessels