

Contrast enhancement of liver lesions in cirrhotic patients: a single institution crossover comparative study of two MR contrast agents. Preliminary results*

Realce por contraste de lesões hepáticas em pacientes com cirrose: estudo cruzado comparativo de dois agentes de contraste para RM realizado em uma única instituição. Resultados preliminares

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Abstract Objective: To prospectively compare full dose gadopentetate dimeglumine (Gd-DTPA) with full dose gadobenate dimeglumine (Gd-BOPTA) in the detection of focal hepatic lesions in patients with chronic liver disease on MRI. **Materials and Methods:** Eight patients with hepatic cirrhosis and a strong suspicion for small hepatocellular carcinoma based on prior MRI underwent contrast-enhanced MR examinations, one with full dose Gd-DTPA and one with full dose Gd-BOPTA. The exams were performed from 72–108 hours apart. Two blinded and independent radiologists evaluated images for lesion number, characterization, enhancement, and subjective preference. **Results:** There was no statistically significant difference between the two studies for lesion detection or characterization. There was 18% increased lesion enhancement for Gd-BOPTA, compared to Gd-DTPA, of the dominant lesion. Both blinded readers subjectively preferred the images using Gd-BOPTA over Gd-DTPA in the majority of cases, based on greater lesion enhancement and better edge definition. **Conclusion:** At equivalent full doses, Gd-BOPTA compared similarly with Gd-DTPA in the detection and characterization of focal hepatic lesions in patients with chronic liver disease. However, Gd-BOPTA was superior for increased lesion enhancement and subjective preference of the reader.

Keywords: MultiHance (Gd-BOPTA); Magnevist (Gd-DTPA); Hepatic lesions.

Resumo Objetivo: Comparar, prospectivamente, gadopentato de dimeglumina (Gd-DTPA) e gadobenato de dimeglumina (Gd-BOPTA), ambos em dose plena, na detecção de lesões hepáticas focais, por meio de RM em pacientes com doença hepática crônica. **Materiais e Métodos:** Oito pacientes com cirrose hepática e forte suspeita de um pequeno carcinoma hepatocelular, baseada em RM anterior, foram submetidos a exames de RM contrastada, um com dose plena de Gd-DTPA e outro com dose plena de Gd-BOPTA. Os exames foram realizados com um intervalo de 72 a 108 horas. Dois radiologistas independentes realizaram avaliação às cegas das imagens, considerando número, caracterização e realce das lesões, além de preferências subjetivas. **Resultados:** Não houve diferença estatisticamente significante entre os dois exames quanto à detecção e caracterização das lesões. Observou-se um incremento de 18% no realce da lesão dominante pelo Gd-BOPTA, em comparação com o Gd-DTPA. Na maioria dos casos, ambos os observadores cegos subjetivamente preferiram as imagens utilizando Gd-BOPTA àquelas com Gd-DTPA, com base no maior realce e melhor definição das margens das lesões. **Conclusão:** Em doses plenas equivalentes, Gd-BOPTA e Gd-DTPA são similares na detecção e caracterização de lesões hepáticas focais em pacientes com doença hepática crônica. Entretanto, o Gd-BOPTA foi superior em relação ao realce da lesão, assim como na preferência subjetiva dos observadores.

Unitermos: MultiHance (Gd-BOPTA); Magnevist (Gd-DTPA); Lesões hepáticas.

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INTRODUCTION

Contrast enhanced MRI is an accurate radiologic examination in the evaluation of focal hepatic lesions⁽¹⁾. Diagnostic performances and safety are two critical measures for the evaluation of MR contrast agents.

Gadobenate dimeglumine (Gd-BOPTA, MultiHance; Bracco Diagnostics, Milan, Italy) is a second-generation gadolinium-based contrast agent (GBCA) that differs

from conventional MR contrast agents, such as gadopentetate dimeglumine (Gd-DTPA, Magnevist; Bayer HealthCare Pharmaceuticals, Berlin, Germany) by its ability to be taken up by hepatocytes following extracellular distribution. Conventional GBCAs are eliminated entirely by renal excretion; whereas, hepatocyte uptake by Gd-BOPTA allows for a small amount (3–5%) of concomitant biliary excretion^(2–5). Thus, Gd-BOPTA behaves similar to other

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MR contrast agents on dynamic images acquired within 10 minutes after administration, and it also serves as a liver-specific contrast media on delayed images, 1 to 4 hours following contrast injection. Moreover, Gd-BOPTA has a two fold greater T1 relaxivity in blood in comparison to conventional contrast agents such as Gd-DTPA, which is thought to be secondary to weak protein binding⁽³⁾.

Prior cross-over studies, in which the same patient receives two different contrast agents at separate times, have been performed comparing full dose (0.1 mmol/kg) Gd-BOPTA and Gd-DTPA⁽⁵⁻⁸⁾. These studies have shown improved lesion detection with Gd-BOPTA in the brain and major arterial systems, largely reflecting the higher R1 (T1 relaxivity). In the liver, Gd-BOPTA has been shown to be an effective contrast media in imaging of focal lesions, with improved detection of neoplastic lesions in the liver^(1,3,9-11). Schneider et al. reported comparable liver lesion detection with half dose (0.05 mmol/kg) Gd-BOPTA and full dose (0.1 mmol/kg) Gd-DTPA in a cross over study⁽¹²⁾. We hypothesize that additional lesions will be visualized with full dose Gd-BOPTA. To our knowledge, no study has been performed to compare these agents at full dose in a study of cross-over design. Thus, we performed a study comparing full dose Gd-BOPTA and Gd-DTPA in a cross-over design in patients with known chronic liver disease and small focal hepatic lesions to compare lesion detection, quantitative lesion enhancement and subjective evaluation of these agents.

MATERIALS AND METHODS

This study was sponsored by Bracco Diagnostics and was approved by our institutional review board. All patients signed an informed consent prior to enrollment into the study. Our study was compliant with the Health Insurance Probability and Accountability Act.

Patients

Eight patients (6 male, 2 female) aged 48–62 (mean 55 years) with known hepatic cirrhosis and potential hepatocellular carcinoma based on prior MRI with half dose

Gd-BOPTA were enrolled in this prospective, intra-individual cross over study between January 2008 and August 2009. Three patients had a history of hepatitis C, three patients had a history of hepatitis C and alcoholic cirrhosis, and two patients had a history of alcoholic cirrhosis.

Two comparator patients (1 male, 1 female; mean 39 years) underwent half dose Gd-BOPTA in comparison with full dose Gd-DTPA to act as a control. One patient had a history of hepatitis C while the other patient had a history of vanishing duct syndrome.

The liver lesions included known regenerative nodules, dysplastic nodules, and small hepatocellular carcinomas. Six patients had known hepatocellular carcinoma, one patient had known regenerative nodules, and five patients had known dysplastic nodules. Of the comparative patients, one patient had regenerative nodules while the other had dysplastic nodules. The diagnosis of regenerative nodule, dysplastic nodule, and hepatocellular carcinoma were based on imaging characteristics only. Blood creatinine levels were obtained prior to enrollment into the study; and patients were to be excluded if their renal function was impaired (GFR less than 60 ml/min/1.73m²) due to the risk of nephrogenic systemic fibrosis with administration of GBCA. Any patient who was unable to give informed consent, had a metallic foreign body or pacemaker, or was pregnant or lactating was excluded.

Eligible patients were scheduled for two identical abdominal MRI examinations using the same field strength at 72–108 hours apart, randomized for the order in which the Gd-BOPTA or Gd-DTPA was administered.

Magnetic resonance imaging

All MRI examinations were performed on 1.5 T (Vision, Symphony, or Avanto; Siemens Medical System, Malvern, PA, USA) or 3.0 T (Trio; Siemens Medical Systems, Malvern, PA, USA) MRI systems using a phased-array torso coil. The patients were given full doses (0.1 mmol per kilogram of body weight) of Gd-BOPTA (MultiHance) or Gd-DTPA (Magnevist). The contrast media was administered by a power injection (Medrad, Pittsburgh, PA,

USA) as a bolus of 0.1 mmol/kg gadolinium chelate at 2 ml/s in all patients. Dynamic post-contrast imaging was obtained with an empiric 18 second delay.

In all patients, standard upper abdomen protocol, including pre-gadolinium and post-gadolinium sequences, was performed. The parameters used for MRI in 1.5 T system were: 2D gradient echo (GE) pre- and post-contrast, in axial plane, in and out-of-phase, TR = 140–200 ms, TE = 4.4 ms / TE = 2.4 ms, flip angle = 80°, section thickness = 8 mm, matrix size = 128 × 256, acquisition time = 20s; 3D GE pre- and post-contrast, axial plane, fat saturation, TR = 4.3 ms, TE = 1.7 ms, flip angle = 10°, section thickness = 3.5 mm, matrix size = 144 × 320, acquisition time = 19 s. In patients examined in 3 T system, the parameters were: 3D GE pre- and post-contrast, axial plane, fat saturation, TR = 3.07 ms, TE = 1.32 ms, flip angle = 13°, section thickness = 3 mm, matrix size = 256 × 256 and acquisition time = 19 s.

Image evaluation

Two independent, expert radiologists evaluated all images. The radiologists were blinded to the type of contrast media utilized, clinical background, and prior radiographic information. Lesion size, location, and probable pathologic diagnosis were determined on T1- and T2- weighted images and on early and late post-gadolinium MR images. Identical T1-weighted sequences were compared between the two studies, at 3 T these were all 3D gradient echo sequences (2) and at 1.5 T the sequences were 2D (6) or 3D (2). Each reader documented subjective preference on lesion delineation and edge definition. Quantitative percent of enhancement was determined on hepatic arterial phase images using the following formula: post-contrast signal intensity - pre-contrast signal intensity/pre-contrast signal intensity. In patients with more than one lesion, signal intensity was performed on the dominant hepatic lesion to determine the degree of enhancement.

Statistical analysis

Differences in diagnostic information findings for each of the readers were compared using the Wilcoxon signed ranks test.

Evaluation of the quantitative data was performed using paired t-tests to determine difference in lesion detection as well as overall enhancement of lesions. All statistical tests were conducted at a significance level of $p < 0.05$ using the statistical software package InStat (InStat 3).

RESULTS

Interreader agreement

There was no statistical difference between the two blinded readers for either the number of hepatic lesions detected or the lesion characterization of scans using Gd-BOPTA and scans using Gd-DTPA ($p = 0.56$).

Lesion detection

The individual readers documented lesion location, characterization, size, and number. No statistically significant differences were observed between the two blinded readers for lesion detection of focal hepatic lesions between full dose Gd-BOPTA and full dose Gd-DTPA (p value > 0.05). Similarly, there were no statistically significant differences when comparing lesion characterization or size between MR examinations completed with Gd-BOPTA and Gd-DTPA (p value > 0.05). When comparing lesion size, there was no statistical difference between full dose Gd-BOPTA and Gd-DTPA (p value > 0.05).

Subjective preference

The findings of the two blinded readers with regards to the lesion delineation, characterization of the lesions, and edge definition suggested a preference for Gd-BOPTA over Gd-DTPA. Reader 1 preferred Gd-BOPTA enhanced MR examinations in all eight cases (100%). Reader 2 preferred Gd-BOPTA enhanced MR examinations in five of the eight cases (62%). In the remaining cases, examination with Gd-DTPA was preferred.

Lesion enhancement

When comparing enhancement of the dominant hepatic lesion, Gd-BOPTA revealed improved enhancement over Gd-DTPA in all eight cases. Gd-BOPTA offered a mean increase of 18.1% (range 1–47%) in signal intensity over Gd-DTPA.

Comparator data with full dose Gd-DTPA and half-dose Gd-BOPTA

In two comparator patients with full dose Gd-DTPA and half-dose Gd-BOPTA, there was no difference in interreader agreement or lesion detection. The patients who received full dose Gd-DTPA showed an 11% greater enhancement than with half dose Gd-BOPTA. Both readers preferred full dose Gd-DTPA to Gd-BOPTA.

DISCUSSION

This study demonstrates that full dose Gd-BOPTA appears to be at least equivalent to full dose Gd-DTPA in detection and characterization of hepatic lesions in patients with underlying hepatic cirrhosis. All of the hepatic lesions detected with Gd-DTPA were also detected with Gd-BOPTA, which mirrors recent literature^(10–12). These studies also demonstrated improved liver-to-lesion contrast on the delayed images with Gd-BOPTA. Although Gd-BOPTA has achieved equal detection of focal hepatic lesions in the dynamic phase of imaging, prior studies have suggested that the addition of delayed phase imaging has added the additional information needed for clinical diagnosis in cases with equivocal dynamic images^(13,14). This latter point was not, however, part of the intent of our study.

Our data does not support the concept that Gd-BOPTA is more sensitive, as we had originally hypothesized, since no additional lesions were detected with Gd-BOPTA. We did, however, document greater lesion enhancement. We found lesion enhancement increased by 18% with full dose Gd-BOPTA compared to full dose Gd-DTPA. This 18% increase is similar to the magnitude of increase previously observed with double dose standard GBCA agents in the evaluation of brain tumors^(12,15). However, double dose GBCA use should be avoided because of the risks of nephrogenic systemic fibrosis (NSF)⁽¹⁶⁾. Because of the increased lesional enhancement, we postulate that with a larger number of patients, additional lesions may be detected with full dose Gd-BOPTA compared to Gd-DTPA. However, this would require further study.

In addition to the increased lesion enhancement, we found a subjective preference of both readers for studies using full

dose Gd-BOPTA. This preference was based on improved lesion delineation and edge definition when using Gd-BOPTA compared with Gd-DTPA. This subjective preference is in line with earlier studies that also showed a similar preference for Gd-BOPTA in MR imaging of the brain^(6,17). We hypothesize that the reason for both the increased lesion enhancement and reader preference with Gd-BOPTA is due to the two-fold increase in T1 relaxivity. This increased T1 relaxivity has been described as due to its lipophilic properties as well as the weak interaction of Gd-BOPTA with serum albumin⁽³⁾.

Given recent literature regarding the efficient use of comparators, two comparator cases were included in this study⁽¹⁸⁾. These two comparator cases demonstrated no difference in lesion detection, however; those patients who received full dose Gd-DTPA showed an 11% greater enhancement than with half dose Gd-BOPTA. Despite these findings of decreased enhancement, prior research has also shown similar lesion detection rate possibly justifying the use of half dose Gd-BOPTA in clinical practice^(10–12).

One other factor in playing a role in lesion detection rate is the magnetic field strength. Prior studies have shown advantages of 3 T imaging over 1.5 T, the most important of which include higher spatial resolution and greater contrast enhancement⁽¹⁹⁾. This translates into better appreciation of small enhancing lesions. It is uncertain what effect the difference in field strength would have on the detection of lesions with these two contrast agents at full or half dose. The authors hypothesize that the difference between the two agents would be accentuated, however, this would require additional research.

The main limitation to our study is the small patient population. Our original intention had been to involve 25 patients in the study; however, between study conception and study implementation the entity NSH was discovered to be associated with GBCA use. The severity of the clinical findings of NSH combined with the association with cumulative GBCA doses rendered in the author's minds that the risks outweighed the potential benefits. Therefore, we severely restricted entrance into the study because of ethical consideration,

and furthermore terminated the study early as substantial differences were not observed among the initial patients. Nonetheless, given the increased lesion enhancement with Gd-BOPTA, we speculate that if our patient population was expanded, there may be a statistical advantage to Gd-BOPTA in the detection of hepatic lesions over conventional contrast media such as Gd-DTPA. Similarly, we did observe qualitative and quantitative advantages of full dose Gd-DTPA over our current practice of half dose Gd-BOPTA.

The safety of Gd-BOPTA was not reported in this study; however, prior studies have demonstrated that Gd-BOPTA is a safe MR imaging contrast agent for use in dynamic and delayed hepatic imaging⁽⁴⁾. Furthermore, multicenter phase studies have followed adverse reactions from Gd-BOPTA have reported no statistical difference between the rates of adverse reactions from Gd-BOPTA versus Gd-DTPA⁽¹⁸⁾. More importantly, to date, we are aware of no reports of NSF with the isolated use of Gd-BOPTA (i.e. no unconfounded cases).

Gd-BOPTA offers at least equivalent detection of focal hepatic lesions in the immediate dynamic phases; however there is improved enhancement of hepatic lesions.

REFERENCES

- Hamm B, Thoeni RF, Gould RG, et al. Focal liver lesions: characterization with nonenhanced and dynamic contrast material-enhanced MR imaging. *Radiology*. 1994;190:417–23.
- Kuwatsuru R, Kadoya M, Ohtomo K, et al. Comparison of gadobenate dimeglumine with gadopentetate dimeglumine for magnetic resonance imaging of liver tumors. *Invest Radiol*. 2001;36:632–41.
- Balci NC, Semelka RC. Contrast agents for MR imaging of the liver. *Radiol Clin North Am*. 2005;43:887–98.
- Spinazzi A, Lorusso V, Pirovano G, et al. Safety, tolerance, biodistribution, and MR imaging enhancement of the liver with gadobenate dimeglumine: results of clinical pharmacologic and pilot imaging studies in nonpatient and patient volunteers. *Acad Radiol*. 1999;6:282–91.
- Rumboldt Z, Rowley HA, Steinberg F, et al. Multicenter, double-blind, randomized, intra-individual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine in MRI of brain tumors at 3 tesla. *J Magn Reson Imaging*. 2009;29:760–7.
- Maravilla KR, Maldjian JA, Schmalfluss IM, et al. Contrast enhancement of central nervous system lesions: multicenter intraindividual crossover comparative study of two MR contrast agents. *Radiology*. 2006;240:389–400.
- Prokop M, Schneider G, Vanzulli A, et al. Contrast-enhanced MR angiography of the renal arteries: blinded multicenter crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine. *Radiology*. 2005;234:399–408.
- Runge VM, Armstrong MR, Barr RG, et al. A clinical comparison of the safety and efficacy of MultiHance (gadobenate dimeglumine) and Omniscan (gadodiamide) in magnetic resonance imaging in patients with central nervous system pathology. *Invest Radiol*. 2001;36:65–71.
- Runge VM, Kenney CM. Phase II double-blind, dose-ranging clinical evaluation of gadobenate dimeglumine in focal liver lesions: with analysis of liver and kidney signal change on early and delayed imaging. *J Magn Reson Imaging*. 2000;11:655–64.
- Petersein J, Spinazzi A, Giovagnoni A, et al. Focal liver lesions: evaluation of the efficacy of gadobenate dimeglumine in MR imaging – a multicenter phase III clinical study. *Radiology*. 2000;215:727–36.
- Pirovano F, Vanzulli A, Marti-Bonmati L, et al. Evaluation of the accuracy of gadobenate dimeglumine-enhanced MR imaging in the detection and characterization of focal liver lesions. *AJR Am J Roentgenol*. 2000;175:1111–20.
- Schneider G, Maas R, Schultze Kool L, et al. Low-dose gadobenate dimeglumine versus standard dose gadopentetate dimeglumine for contrast-enhanced magnetic resonance imaging of the liver: an intra-individual crossover comparison. *Invest Radiol*. 2003;38:85–94.
- Grazioli L, Morana G, Caudana R, et al. Hepatocellular carcinoma: correlation between gadobenate dimeglumine-enhanced MRI and pathologic findings. *Invest Radiol*. 2000;35:25–34.
- Grazioli L, Morana G, Federle MP, et al. Focal nodular hyperplasia: morphological and functional information from MR imaging with gadobenate dimeglumine. *Radiology*. 2001;221:731–9.
- Yuh WT, Fisher DJ, Engelken JD, et al. MR evaluation of CNS tumors: dose comparison study with gadopentetate dimeglumine and gadoteridol. *Radiology*. 1991;180:485–91.
- Heinz-Peer G, Neruda A, Watschinger B, et al. Prevalence of NSF following intravenous gadolinium-contrast media administration in dialysis patients with endstage renal disease. *Eur J Radiol*. 2010;76:129–34.
- Rowley HA, Scialfa G, Gao PY, et al. Contrast-enhanced MR imaging of brain lesions: a large-scale intraindividual crossover comparison of gadobenate dimeglumine versus gadodiamide. *AJNR Am J Neuroradiol*. 2008;29:1684–91.
- Luce BR, Kramer JM, Goodman SN, et al. Rethinking randomized clinical trials for comparative effectiveness research: the need for transformational change. *Ann Intern Med*. 2009;151:206–9.
- Ramalho M, Altun E, Herédia V, et al. Liver MR imaging: 1.5T versus 3T. *Magn Reson Imaging Clin N Am*. 2007;15:321–47.