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Original article

Liver specific magnetic resonance imaging contrast medium for evaluation of focal liver lesions – Initial experience at a service hospital

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ABSTRACT

Background: Contrast enhanced MRI is today considered the investigation modality of choice in detection and characterization of focal liver lesions. The conventional MRI contrast media like Gadolinium (Gd) chelates undergo elimination through the urinary pathway and are not selectively concentrated or metabolized in the liver. Gadobenate dimeglumine (Chemical name: Gadolinium-BOPTA) is a promising newer liver specific MRI contrast medium having additional properties of selective uptake and biliary excretion by hepatocytes. Our study was designed as a pilot study to evaluate the utility of Gd-BOPTA in detection and characterization of focal liver lesions.

Methods: Fifty-three consecutive patients with focal liver lesions (excluding only simple hepatic cysts) detected on ultrasonography and CT abdomen, were prospectively subjected to standardized MRI protocol for the liver, using Gd-BOPTA as the intravenous contrast medium. An additional T1W axial scan of the liver was incorporated in the study protocol, at a delay of 2 h post-contrast, in all patients.

Results: In the study population, the combination of USG and contrast enhanced CT abdomen findings were adequate to reach a definitive diagnosis in 70% of the patients. The liver specificity of Gd-BOPTA contributed to improved lesional characterization in 9/50 patients (18%) on the delayed phase images.

Conclusion: The study revealed that the liver specific properties of Gd-BOPTA can be used to obtain additional information to improve characterization of focal hepatic lesions, when delayed phase scans are included in the study protocol.

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Introduction

Focal liver lesions represent a spectrum of lesions ranging from harmlessly benign to aggressively malignant, whose accurate characterization has prognostic and therapeutic

implications.¹ The past two decades have seen widespread use of ultrasonography (USG), contrast enhanced computerized tomography (CECT) and magnetic resonance imaging (MRI).² While USG remains the modality of choice for screening purposes in liver imaging, CECT liver performed

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using multi-detector scanners with volumetric data acquisition and multi-planar reconstruction capabilities has been the preferred hepatic imaging modality.^{3,4} The major drawbacks of CECT are its inherent radiation hazard and side-effects of iodinated contrast.

The role of MRI is today changing from a limited problem-solver technique to being a first-line hepatic imaging modality.^{5,6} Using faster imaging sequences and improved software algorithms, anatomic detail and lesion-to-liver contrast can be optimized by dynamic studies facilitating better detection and characterization of liver lesions than USG/CECT.⁷ Liver specific MR contrast media take advantage of the affinity of certain compounds to concentrate in hepatocytes or Kupffer cells. Gadobenate dimeglumine (Gd-BOPTA) is one such intravenously administered liver specific MRI contrast medium which has proven selective uptake by hepatocytes and subsequent biliary excretion attributed to its chemical composition.^{2,4} Our study was designed as a single-center pilot study to evaluate the utility of Gd-BOPTA as a liver specific MRI imaging contrast agent for characterization of focal liver lesions.

Material and methods

Patients

Fifty-three consecutive patients with focal liver lesions detected on USG and CECT at the Department of Radio-diagnosis of a tertiary care referral hospital were included in the study, for further imaging of the liver lesions by Gd-BOPTA enhanced MRI Liver. Hospital ethical committee clearance for the study was obtained for the project prior to its commencement and informed consent of the patient for contrast enhanced imaging studies and lesional FNAC (where applicable) was taken in writing for each study. Patient exclusion criteria were pregnant women, patients less than 18 years (manufacturers recommendation), patients with poor cardio-respiratory reserve and patients with cardiac pacemakers/non-compatible implants. Simple hepatic cysts, conforming to standard USG criteria, were excluded. Post-procedurally, all patients were evaluated for immediate side-effects and by standard liver and kidney function tests between 24 and 48 h.

Contrast medium and equipment

USG was performed on a GE Logiq 3 machine using 3.5 MHz sector probe in all patients. All patients also underwent dual-phase CECT abdomen on a helical CT scanner (GE HiSpeed CTi, USA) using 5 mm axial sections at a pitch factor of 1.0, 120 kV and 280 mA with breath-hold time of 12–16 s. Non-ionic iodinated contrast medium (iodine content 300 mg%) at dose of 1.5 ml/kg patient body weight was administered intravenous (IV) using a pressure injector at the rate of 3 ml/s. The MRI studies were performed on a super-conducting clinical imaging equipment of field strength 1.0 T (Magnetom Harmony; Siemens, Germany). Patients were administered 0.1 mmol/kg (0.2 ml/kg) of gadobenate dimeglumine (Gd-BOPTA) as a single-bolus IV injection using a dual-head pressure injector at the rate of 2 ml/s followed by a 10 ml saline chaser.

Imaging protocols

The liver was imaged using a standard body coil, with section thickness of 8 mm on all sequences. The MR imaging protocols included acquisition of T2-weighted and T1-weighted single-breath-hold sequences, supplemented with a non-breath-hold double T2-weighted sequence. A baseline pre-contrast T1-weighted gradient-echo breath-hold sequence was done in all patients. Dynamic phase images were obtained at arterial phase (30–45 s), portal venous phase (60–90 s) and equilibrium phase (4–5 min). Delayed phase images were obtained after 2 h.

Image analysis

Two experienced radiologists without access to final diagnosis of the patients performed the image assessment. Images were assessed for image quality and graded as poor/satisfactory/good. Lesion size, segmental localization (Couinaud–Bismuth system) and enhancement characteristics were documented. Delayed images were analyzed for lesion-to-liver contrast and for detectable contrast excretion into the biliary system. Three patients with poor image quality were excluded from the database.

Results

Of the fifty patients analyzed, 31 were men (62%) and 19 were women (38%), in age range between 23 and 78 years, with mean age of 48.4 years. A relatively later mean age incidence at 52 years in women was seen vis-a-vis 46.6 years in males. Thirty-four (68%) patients had solitary lesion, and sixteen (32%) patients had multiple lesions, with seven of these patients having more than ten lesions. Twenty-seven (54%) patients had pathological correlation attempted by image-guided fine-needle aspiration cytology (FNAC), while six (12%) patients underwent surgery and pathology correlation, performed between 2 and 10 days after MR examination. The remaining seventeen (34%) patients did not require intervention as definitive diagnosis of benign lesions (hemangiomas, focal fatty changes and segmental fibrosis) was reached on the basis of composite (USG, CECT and dynamic CE-MRI) imaging findings, and were followed up on USG. The benign lesions comprised thirty-four patients (68%) and included abscesses (14), hemangiomas (13), focal fatty changes of liver (3), hydatid cysts (2), segmental fibrosis (1) and regenerating nodule (1). Malignant lesions encountered in our study comprised of sixteen patients (32%), including seven metastases, four hepato-cellular carcinoma (HCC), three carcinoma gallbladder with hepatic infiltration and two patients of central cholangiocarcinoma.

Of the 16 patients with malignant etiology, 9 (56%) patients exhibited arterial phase enhancement, whereas delayed persistent enhancement was noted only in 7 patients (44%). Evidence of contrast enhancement within the lesions was seen in the portal venous phase as compared to the pre-contrast images in all patients (100%). Significantly, all patients who were subsequently confirmed as HCC/regenerating nodule had shown delayed enhancement (Fig. 1), whereas most patients of metastases and local infiltration of

Fig. 1 – A–C: focal heterogeneously echogenic nodule of 4 cm size seen in Segment V was noted on USG in a 58-year-old male non-cirrhotic patient under evaluation for weight loss. CECT (A): hypodense, minimally enhancing lesion (thin arrow) in Segment V. Contrast enhanced T1W MRI – arterial phase axial image (B) shows heterogenous enhancement of lesion. T1W MRI – 2 h delayed phase coronal image (C) showing persistent central enhancement within the lesion (thin arrow); also noted is hyperintensity within the gallbladder (thick arrow) indicative of biliary excretion of Gd-BOPTA. Final diagnosis: HCC (FNAC proven).

carcinoma gallbladder did not exhibit this phenomenon. The delayed imaging performed at 2 h after contrast administration revealed contrast opacification of the biliary tract and/or gallbladder (Fig. 2) in 38 patients (76%), of which 8 patients were proven to have malignant etiology on histopathology. Thirty out of the 34 patients with benign etiologies had detectable contrast excretion into the biliary channels, which formed approx 88% of this subset of patients as against the relatively lower 50% of patients with malignant etiology.

All patients tolerated the intravenous administration of Gd-BOPTA, with no symptoms related to cardio-vascular, respiratory, gastro-intestinal tract or central nervous systems attributable to contrast toxicity in immediate post-contrast period. None of our patients had elevation of blood pressure or pulse rate on clinical assessment performed approximately 10 min after Gd-BOPTA administration. Standard hepatic and renal function laboratory tests performed within 48 h did not show significant alteration in the levels of serum bilirubin, liver enzymes (ALT, AST & Alkaline phosphatase), blood urea or serum creatinine.

The diagnostic capability comparisons between CECT abdomen versus MRI, and the augmentation of diagnostic capability on upscaling the MRI study from the baseline non-contrast study to dynamic CE-MRI and further supplementation of the information using delayed scanning performed at 120 min, are depicted in Table 1. Used in combination, USG and CECT abdomen were adequate to reach a definitive imaging diagnosis in approx 70% of the patients. Baseline

unenhanced MRI images could offer specific diagnoses in entities such as hemangioma, fatty changes (deposition/sparing) and biliary tract neoplasms. The overall correctness of diagnosis, by consensus of two observers, increased from 48% in the unenhanced MRI scan to 86% on completion of the dynamic CE-MRI.

The liver specificity of the contrast medium was amplified in 5 patients (10%) in the delayed imaging subset, in whom the findings of retained contrast enhancement within lesion contributed to the definitive diagnosis of HCC, regenerating nodule (Fig. 3) and chronic abscess (Fig. 4). In another 4 (8%) patients, two of HCC and one each with segmental fibrosis and complicated hydatid cyst, the delayed imaging findings reinforced the diagnoses made on the unenhanced and dynamic CE-MRI.

Discussion

Focal liver lesions have always been an imaging challenge because of the wide divergence in management strategies based on lesion etiology. Malignant neoplastic lesions may benefit from surgical excision or interventional therapy, whereas 'benign' neoplastic lesions often do not require any treatment and infective lesions respond to medical therapy or surgical drainage.¹ Therefore, the ability to accurately differentiate between benign and malignant lesions would form the cornerstone of any form of hepatic imaging.² Currently, there

Fig. 2 – T1W post-contrast image spectrum at 2 h interval, showing hyperintensity within the gallbladder (thick arrow) and/or CBD (curved arrow) indicative of biliary excretion of Gd-BOPTA.

Table 1 – Provisional etiological diagnoses by CECT/MRI as compared with final diagnoses arrived at by imaging/FNAC/surgery.

S. no.	Final diagnosis	No. of cases	CECT abdomen	Unenhanced MRI	Dynamic CE-MRI	Delayed phase @2 h	Contribution of delayed phase findings to final diagnosis	Comments on utility of delayed phase images
1	Abscess	14	10	5	12	14	2 ^a	Persistent wall enhancement and central necrosis
2	Hemangioma	13	11	11	13	13	—	—
3	Focal fatty change	3	2	3	3	3	—	—
4	Hydatid cyst	2	1	1	2	2	1 ^b	Cyst pseudo-capsule highlighted
5	Segmental fibrosis	1	—	—	1	1	1 ^b	Persistent liver enhancement with non-enhancing scar
6	Regenerating nodule	1	—	—	—	1	1 ^a	Delayed central persistent enhancement
7	HCC	4	2	—	2	4	2 ^a & 2 ^b	Persistent central enhancement
8	Carcinoma GB	3	2	1	3	3	—	—
9	Cholangio-Ca	2	2	1	2	2	—	Poor contrast excretion into biliary tract
10	Metastases	7	5	2	6	6	—	Persistent liver enhancement, making lesions highlighted
Total		50	35 (70%)	24 (48%)	44 (88%)	49 (98%)	9 (18%)	

a Indicates number of patients in whom additional information derived from delayed scan directly contributed to final diagnosis.

b Indicates number of patients in whom additional information derived from delayed scan reinforced diagnosis as made on dynamic CE-MRI.

is no consensus regarding optimal strategy for liver imaging. Modalities are often decided based on a combination of clinicians request, availability of equipment/expertise and economics. Most diagnostic centers use USG and CECT augmented with USG/CT guided biopsy, with MRI used as a problem solving modality in selected patients.³

MR imaging has the single-window potential to provide comprehensive and accurate information in hepatic imaging.¹ It can detect diffuse and focal liver lesions, with the added advantage of tissue characterization and multi-planar anatomy, thus obviate need for other imaging modalities.⁶ The augmentation of imaging with MRI contrast media further provides essential information regarding vascular dynamics of any lesion, comparable to the multi-phase CECT studies. MR imaging as a diagnostic technique has advantages over CT in terms of diagnostic sensitivity and tissue specificity, without the concerns of risks related to iodinated contrast media and radiation.⁷ CT radiation risk is an invisible but potent hazard with an estimated attributable cancer mortality ranging from 0.08% in persons below 45 years to 2% in patients between 45 and 70 years.⁸ Similarly the risk of iodinated contrast induced nephropathy increases from 2% in a general population to 9–40% in patients with diabetes mellitus and/or pre-existing medical renal disease.⁹ Thus the concept of using MRI as a first-line modality for ‘cost-effective’ hepatic imaging to enable accurate diagnosis, is gaining favor worldwide.⁶

Contrast enhancement of tissues is assessed on T1-weighted (T1W) sequences using gadolinium chelates. Gadolinium has paramagnetic properties shortening tissue T1 relaxation times, visible as increased MR signals. Gadolinium chelates are clinically safe and pharmacologically inert, with minimal risk of serious anaphylaxis. The liver has a unique dual blood supply, receiving 20–30% flow from the hepatic artery and 70–80% supply from the portal vein. Focal liver lesions can therefore potentially be differentiated on the basis

of their selective source of blood supply reflected in the time-intensity contrast enhancement curves on dynamic post-gadolinium T1W imaging.^{10,11}

Liver specific MR contrast media take advantage of affinity of certain compounds to concentrate in hepatocytes or Kupffer cells. Gadobenate dimeglumine (Gd-BOPTA) is an intravenously administered liver specific MRI contrast medium, which has proven selective uptake by hepatocytes and subsequent biliary excretion.² Other MRI contrast agents such as Super-Paramagnetic Iron Oxides (SPIO) and Manganese (Mn) based compounds produce enhancement based on their uptake by reticulo-endothelial system and functioning hepatocytes respectively; however, these contrast media cannot be used for performing dynamic CE-MRI.¹¹

The active component of gadobenate dimeglumine is gadobenic acid chelated with dimeglumine to form an octadentate molecule incorporating the basic paramagnetic ion gadolinium. Due to its chemical composition containing a benzene ring on its chelate, it is secreted into the bile by canalicular organic ion transporter system.⁵ Gd-BOPTA thus has extra-cellular fluid space distribution and biokinetics similar to conventional gadolinium molecules, with its additional properties of selective hepatic concentration and biliary excretion as bonus.^{3,11} It is now established that upto 5% of a parenterally administered dose of Gd-BOPTA in humans is excreted through the biliary tract.^{2,4} The persistence of enhanced liver parenchyma and detectable excretion of Gd-BOPTA seen as hyperintensity of the biliary tracts/gall-bladder on the delayed images in 37 patients (74%) in our study was definitive evidence supporting liver specificity of the contrast medium.

Benign focal hepatic lesions such as cysts, hemangioma, hamartoma and focal nodular hyperplasia may be incidentally detected in upto 20% of adult population. With advent of multi-detector CT scanners, smaller lesions are being

Fig. 3 – A–C: T1W post-contrast image spectrum showing persistent contrast enhancement by hepatocytes on imaging at 2 h: A – abscess; B – multiple metastases; C – regenerating nodule.

detected more frequently, with lesions smaller than 15 mm seen on CT being benign in over 80% of patients.¹² In our study, only 68% of patients had benign lesions, primarily because of the exclusion criteria exercised in respect of simple cysts detected on USG/CT. While the most common malignant liver lesions are metastases, the common primary hepato-biliary malignant lesions are hepato-cellular carcinoma (HCC) and intra-hepatic cholangio-carcinoma. HCC is a known complication of cirrhosis with incidence of 1–2% in cirrhotic patients.¹³ Out of the 32% (16/50) patients having malignant lesions in our study, 7 patients had metastatic disease while there were 4 patients of HCC, 3 patients of carcinoma GB and 2 patients with intra-hepatic cholangio-carcinoma.

The sensitivity, specificity and accuracy of unenhanced MR imaging (without MR contrast media administration) for lesion characterization were only 80%, 77% and 84% in a study by Pirovano et al² which showed a significant increase to 93%, 92% and 90% on contrast imaging. This study also noted that the delayed images at 60–120 min showed persistence of liver enhancement. In a Phase-III multi-center clinical study on MRI of liver lesions by Petersein et al³ Gd-BOPTA enhanced MR imaging yielded a change in diagnostic conclusion in nearly 50% cases. In addition, the average size of the smallest detected lesion was reduced by approximately 10–15% on evaluation of the delayed post-contrast MR images. In a comparative study on the efficacy of liver specific MRI contrast media in detection of liver

Fig. 4 – A–C: 47-year-old male patient who presented with vague pain right upper quadrant of the abdomen. USG revealed a complex mass in Segment 7 of the liver (A), which was seen to be a thick-walled cavitating lesion on CECT abdomen (B). Dynamic contrast enhanced T1W axial portal venous phase image shows lesion with enhancing wall and central region devoid of signal (C) consistent with chronic abscess. Study shows hepatic and vascular contrast enhancement similar to conventional MRI contrast media.

metastases, Del Frate observed that there was a demonstrable increase in contrast-to-noise ratio between normal liver and lesions on Gd-BOPTA enhanced T1-weighted images obtained during the delayed phase of the study, resulting in a small but definite increase in liver metastases detection.¹⁴ Both studies concluded that Gd-BOPTA can be utilized in all applications as for standard extra-cellular MR contrast media, and have advantage in liver imaging with their capability for providing both dynamic contrast enhancement patterns as well as hepatocyte-specific information on delayed phase imaging.

In the present study, we observed that the overall correctness of diagnosis, by consensus of two observers, increased from 48% in the unenhanced MRI scan to 86% on completion of the dynamic CE-MRI, which is comparable with that of any other contemporary study using conventional MRI contrast media.^{2,10,13,15} The liver specificity of the contrast medium was amplified in 5 (10%) patients in the delayed imaging subset, in whom the findings of retained lesional contrast contributed to the definitive diagnosis of HCC, regenerating nodule and chronic abscess (Fig. 4). In another 4 (8%) patients, two of HCC and one each with segmental fibrosis and complicated hydatid cyst, the delayed imaging findings reinforced the diagnoses made on the pre-contrast and dynamic CE-MRI (Fig. 3). This observation is similar to findings reported previously by Pirovano et al.,² Petersein et al.³ and Del Frate et al.¹⁴

Persistent lesional enhancement observed in this study in the delayed imaging sequences, which was noted in 7 patients (14%) has not been found reported previously in literature. Significantly, all patients who were subsequently confirmed as HCC/regenerating nodule and two patients with chronic abscess had shown delayed enhancement, raising a possibility of using this enhancement pattern as an indicator of etiology. The HCC/regenerating nodule lesions displayed a central heterogenous enhancement pattern while the chronic abscesses showed homogenous enhancement of their thickened wall. The regenerating nodule was a false positive diagnosis in this study, having been diagnosed as HCC on imaging, but proven to contain only normal hepatocytes on FNAC. Conspicuously, majority of metastases and the local infiltration from carcinoma gallbladder did not exhibit this phenomenon.

The following limitations were noted during the course of this 'pilot' study. Firstly, the sample size was small for conclusive assessment of MRI contrast signal characteristics and statistical correlates for the diverse range of pathologic entities. Secondly, it was not possible to compare the signal intensity produced by the Gd-BOPTA compound as against that of the conventional (non-liver specific) contrast media in use, as none of the patients underwent repeat MRI studies. The requirement of delayed imaging, in addition to the conventional pre-contrast and post-contrast dynamic sequences has practical implications related to cost, time and technologist.⁴ Increasing the duration of the study reduces its tolerance, especially in patients with poor general health. Nevertheless, delayed imaging yields additional information without any increased contrast dosage and is a useful add-on capability, to be used judiciously.

In conclusion, Gd-BOPTA (Gadobenate Dimeglumine) has extra-cellular distribution, pharmacokinetics and clinical safety comparable to conventional MR contrast media. It has

a definite liver specific role as seen in the delayed imaging at 120 min, when liver tissue having functional hepatocytes showed persistent enhancement and biliary excretion. This advantage is achieved using established imaging sequences, without increasing contrast doses or any software modification. The diagnostic confidence and lesional characterization for focal liver lesions on using Gd-BOPTA for dynamic contrast enhanced MRI supplemented with a delayed imaging protocol was found to be superior to CECT abdomen.

Conflicts of interest

All authors have none to declare.

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