Liver-specific magnetic resonance contrast medium in the evaluation of chronic liver disease

Aplicações do contraste hepato-específico de ressonância magnética nas hepatopatias crônicas

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ABSTRACT

The hepatobiliary-specific contrast medium (gadoxetic acid – Primovist®) is primarily used to improve detection and characterization of focal hepatic lesions, such as in chronic liver disease patients with suspected hepatocellular carcinoma. Since the contrast medium is selectively taken up by functioning hepatocytes in the late hepatobiliary phase, it helps to detect typical hepatocellular carcinoma, which show low signal intensity on this phase. This imaging feature also assists in differentiating regenerative/dysplastic nodules from early hepatocellular carcinomas (with over 90% accuracy), as well as hypervascular hepatocellular carcinomas from arterial pseudo-enhancement foci. Future perspectives include its use in quantification of hepatic function and fibrosis.

Keywords: Liver neoplasms/diagnosis; Liver diseases/diagnosis; Carcinoma, hepatocellular/diagnosis; Contrast media/utilization; Magnetic resonance imaging/methods

INTRODUCTION

Magnetic resonance imaging (MRI) is a well-established test to assess focal liver lesions. However, up to 60% of malignant nodules may not be detected or characterized by MRI, mainly those smaller than 1.0cm and in cirrhotic livers.(1,2)

Liver-specific contrast media were developed to increase sensitivity and specificity of MRI in assessing focal lesions, as well as to overcome some of the limitations observed with extracellular contrast media. Among the liver-specific contrast media currently available, only gadoxetic acid (Gd-EOB-dTPA, Primovist®, Bayer Schering, Berlin, Germany) is approved for clinical use in Brazil.

PHYSICAL CHEMICAL PROPERTIES AND BIOAVAILABILITY

Gd-EOB-dTPA is a liver-specific, gadolinium-based paramagnetic contrast, with combined properties of hepatocyte perfusion and selectivity. It was primarily developed to increase detection and characterization of focal hepatic lesions. After intravenous administration, Gd-EOB-dTPA is quickly distributed in the vascular/interstitial compartment, allowing for a dynamic, multiphase study (arterial, portal and equilibrium phases).

Approximately 50% of the injected dose of Gd-EOB-dTPA is selectively captured by functioning hepatocytes and later excreted through bile, enabling acquisition of a late hepatobiliary phase, approximately 10-20 minutes after its injection. In this stage, hepatocyte-free lesions (or lesions with dysfunctional hepatocytes) show low MRI signal intensity (dark images on a bright liver), with...
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Due to its hepatocyte specificity, the recommended dose of gadolinium is up to four times lower than that recommended for extracellular contrast media.\textsuperscript{(3-5)}

The high contrast uptake is due to the lipophilic properties of Gd-EOB-dTPA, favoring its passive diffusion by molecular transporters OATP1, which are in the basolateral membrane of normal hepatocytes.\textsuperscript{(6,7)}

After uptake by hepatocytes, Gd-EOB-dTPA is eliminated by biliary (50%) and urinary tracts (50%). At molecular level, biliary excretion is dependent upon the molecular transporter MPR2 that is present on the cell canalicular membrane.\textsuperscript{(6,7)}

CLINICAL USE IN CHRONIC LIVER DISEASE

Hepatocellular carcinomas (HCC) can be diagnosed in a non-invasive manner, by means of imaging tests in patients at increased risk. These lesions typically present intense arterial enhancement, with washout in venous and equilibrium phases both in computerized tomography (CT) and MRI.\textsuperscript{(8,9)}

The presence of fat or pseudocapsule (peripheral enhancement mimicking a real capsule) in late phases increases reliability of diagnosis. Complementary findings in MRI include high-signal intensity on T2 and restricted diffusion of water molecules.

Different patterns for HCC were described after injection of Gd-EOB-dTPA, depending on expression of the molecular transporter OATP1. Since most HCC do not present with functioning hepatocytes, approximately 80 to 90% show low signal intensity in hepatobiliary phase in relation to the surrounding hepatic parenchyma\textsuperscript{(10,11)} (Figure 1).

However, about 10 and 20% of moderately or well-differentiated HCC present an increased expression of OATP1 transporter, leading to isointensity or hyperintensity in relation to the adjacent hepatic parenchyma.\textsuperscript{(10,11)}

In approximately 10% of HCC cases, mainly in small lesions, low signal intensity in hepatobiliary phase may be observed with no hypervascular pattern in the arterial phase, or hyperintensity on T2 and diffusion-weighted images.\textsuperscript{(12)}

EARLY HEPATOCELLULAR CARCINOMA VERSUS REGENERATIVE/DYSPLASTIC NODULE

The concept of early HCC described by the Liver Cancer Study Group of Japan and accepted worldwide, still leads to confusion between Japanese and Western pathologists.\textsuperscript{(13-16)} Although several molecular markers were described for diagnosing early HCC, with high diagnosis rate when used together, the accurate differentiation between dysplastic nodules and early HCC still requires identification of stromal invasion. Therefore, this differentiation is often impossible through biopsy, unless stromal invasion is included in the specimen.\textsuperscript{(17-19)}

This differentiation in imaging tests used to be a challenge, even with advanced techniques, such as CT during liver arteriography or CT portography.

MRI with liver-specific contrast has become a true landmark in this field. Assuming that early HCC usually shows low signal intensity during the hepatobiliary phase, and that the dysplastic nodule shows iso/hypersignal (Figure 2), the diagnostic accuracy for early HCC today is over 95\%.\textsuperscript{(20-22)}

Moreover, some studies that followed the natural course of hypovascular nodules presenting low signal intensity in the hepatobiliary phase showed that even if early HCC is ruled out in biopsy, it is very likely that this nodule will become hypervascular and develop into a typical HCC in the future.\textsuperscript{(23-25)}

In other words, even if the biopsy rules out the diagnosis of early HCC, hypovascular nodules showing

Figure 1. MRI with liver-specific contrast medium in a chronic liver disease patient showing a typical hepatocellular carcinoma on the left lobe. In the arterial phase (A) the lesion is predominantly hypervascular, while in the late hepatobiliary phase it presents a (B) predominant low signal intensity

Figure 2. MRI with liver-specific contrast in a chronic liver disease patient showing lesion with characteristics of dysplastic nodule on the left lobe. Lesion shows hyperintensity in pre-contrast phase (A), and iso/hyperintensity in late hepatobiliary phase (B)
low signal intensity in the hepatobiliary phase can be considered as such for therapy planning, because the risk of malignant changes is very high.

**HYPERVERSAL CARCINOMA VERSUS PSEUDOLESION WITH ARTERIAL ENHANCEMENT**

Arterioporal shunts can mimic hypervascular HCC in conventional MRI and CT studies. These shunts are observed more often in cirrhotic livers as hypervascular lesions ranging between 0.5 and 2.0cm in size, usually without significant expression in any other sequence of the exam.\(^{26,27}\)

However, up to approximately 50% of hypervascular foci in cirrhotic livers actually correspond to HCC and their characterization without repeated exams is a challenge. Today, this differentiation is possible with liver-specific contrast medium, because the shunts correspond to areas of preserved parenchyma (with isointensity to the remaining liver in the late hepatobiliary phase), while most HCC do not show functioning hepatocytes (with low signal intensity in late hepatobiliary phase)\(^{27,28}\) (Figure 3).

![Figure 3. MRIs with liver-specific contrast medium of two chronic liver disease patients. The first patient shows nodular hypervascular focus on segment VII (A), with isointensity to the rest of the parenchyma in late hepatobiliary phase (B), indicating arterioporal shunt. The second patient shows a hypervascular nodular focus in the caudate lobe (C), with low signal intensity in late hepatobiliary phase (D), indicating a small hepatocellular carcinoma](image)

**PERSPECTIVE**

Recent animal studies have suggested that MRI with liver-specific contrast medium might plays an important role in quantification of liver fibrosis. Tsuda et al. showed prolonged peak enhancement and slower washout of Gd-EOB-dTPA in rats with non-alcoholic steatohepatitis when compared to rats with simple steatosis. Moreover, a correlation between the level of fibrosis and the prolonged enhancement peak and washout period was demonstrated.\(^{29,30}\)

Another use of Gd-EOB-dTPA still under investigation is the quantitative assessment of liver function.\(^{31-37}\) Its main advantages are the non-invasive assessment and the regional quantification of liver function, potentially useful to predict residual function in patients that will undergo partial hepatectomy. Gd-EOB-dTPA can also be used to diagnose early liver failure and other parenchymal manifestations of post-transplant complications.\(^{38}\)

**CONCLUSION**

Gadoxetic acid as a liver-specific contrast medium has been increasingly used in chronic liver disease patients, mainly to assess hepatocellular carcinomas and to differentiate it from other focal lesions.

Future perspectives include its use in quantification of fibrosis and liver function.

**REFERENCES**

1. Chanyaputhipong J, Low SC, Chow PK. Gadoxetate Acid-Enhanced MR Imaging for HCC: A Review for Clinicians. Int J Hepatol. 2011;2011:489342.

2. Paulet D, Teixtor J, Bachmann R, Conrad R, Flacke S, Layer G, et al. Hepatocellular carcinoma: detection with gadolinium- and ferumoxides-enhanced MR imaging of the liver. Radiology. 2002;222(1):73-80.

3. Weinmann HJ, Schuhmann-Giampieri G, Schmitt-Willich H, Vogler H, Frenzel T, Gries H. A new lipophilic gadolinium chelate as a tissue-specific contrast medium for MRI. Magn Reson Med. 1991;22(2):233-7; discussion 242.

4. Hamm B, Staks T, Müller A, Bollow M, Taupitz M, Frenzel T, et al. Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. Radiology. 1995;195(3):785-92.

5. Reimer P, Rummeny EJ, Shamsi K, Balzer T, Daldrup HE, Tombach B, et al. Phase II clinical evaluation of Gd-EOB-DTPA: dose, safety aspects, and pulse sequence. Radiology. 1996;199(1):177-83.

6. van Montfoort JE, Stieger B, Meier JK, Weinmann HJ, Meier PJ, Fattinger KE. Hepatic uptake of the magnetic resonance imaging contrast agent gadoxetate by the organic anion transporting polypeptide Oatp1. J Pharmacol Exp Ther. 1999;290(1):153-7.

7. Libra A, Fernetti C, Lorussolo V, Visigalli M, Anelli PL, Staud F, et al. Molecular determinants in the transport of a bile acid-derived diagnostic agent in tumoral and nontumoral cell lines of human liver. J Pharmacol Exp Ther. 2006;319(2):809-17.

8. Bartolozzi C, Battaglia V, Bozzi E. HCC diagnosis with liver-specific MRI--close to histopathology. Dig Dis. 2009;27(2):125-30. Review.

9. Ba-Ssalamah A, Uffmann M, Saini S, Bastai N, Herold C, Schima W. Clinical value of MRI liver-specific contrast agents: a tailored examination for a confident non-invasive diagnosis of focal liver lesions. Eur Radiol. 2009;19(2):342-57. Review.

10. Kim SH, Kim SH, Lee J, Kim MJ, Jeon HY, Park Y, et al. Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol. 2009;192(6):1675-81.

11. Fenrics BB, Loddenkemper C, Huppertz A, Valdeig S, Stroux A, Seja M, et al. Qualitative and quantitative evaluation of hepatocellular carcinoma and cirrhotic liver enhancement using Gd-EOB-DTPA. AJR Am J Roentgenol. 2009;193(4):1053-60.
12. Ahn SS, Kim MJ, Lim JS, Hong HS, Chung YE, Choi JY. Added value of gadoxetic acid-enhanced hepatobiliary phase MR imaging in the diagnosis of hepatocellular carcinoma. Radiology. 2010;255(2):459-66.

13. Kudo M. Early hepatocellular carcinoma: definition and diagnosis. Liver Cancer. 2013;2(2):69-72.

14. The general rules for the clinical and pathological study of primary liver cancer. Liver Cancer Study Group of Japan. 3rd ed. Tokyo: Kanehara, 2010.

15. Kojiro M. Diagnostic discrepancy of early hepatocellular carcinoma between Japan and West. Hepatol Res. 2007;37 Suppl 2:S121-4.

16. Ahn SS, Kim MJ, Lim JS, Hong HS, Chung YE, Choi JY. Added value of gadoxetic acid-enhanced hepatobiliary phase MR imaging in the diagnosis of hepatocellular carcinoma. Radiology. 2010;255(2):459-66.

17. Kudo M. Early hepatocellular carcinoma: definition and diagnosis. Liver Cancer. 2013;2(2):69-72.