REVIEW

THEMATIC REVIEW: TRANSPLANTATION

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

RESUMO

O contraste hepato-específico (ácido gadoxético – Primovist®) tem como utilidade principal melhorar a detecção e a caracterização de lesões hepáticas focais, por exemplo, em hepatopatas crônicos com suspeita de hepatocarcinoma. Por apresentar captação seletiva por hepatócitos funcionantes na fase hepatobiliar tardia, auxilia na detecção de hepatocarcinomas típicos – a maioria dos quais apresentando hipossinal nessa fase. Essa característica de imagem também auxilia na diferenciação entre nódulos regenerativos/displásicos e hepatocarcinomas precoces (com mais de 90% de acurácia), e entre hepatocarcinomas hipervascularizados e focos de pseudorrealce arterial. Perspectivas futuras promissoras incluem sua utilização na quantificação de função e de fibrose hepáticas.

Descritores: Neoplasias hepáticas/diagnóstico; Hepatopatias/diagnóstico; Carcinoma hepatocelular/diagnóstico; Meios de contraste/utilização; Imagem por ressonância magnética/métodos

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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liver/lesion enhancement, improving the diagnostic capability of the test.

Due to its hepatocyte specificity, the recommended dose of gadolinium is up to four times lower than that recommended for extracellular contrast media.[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.[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.[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.[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[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.[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.[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.[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.[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%.[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.[23-25]

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

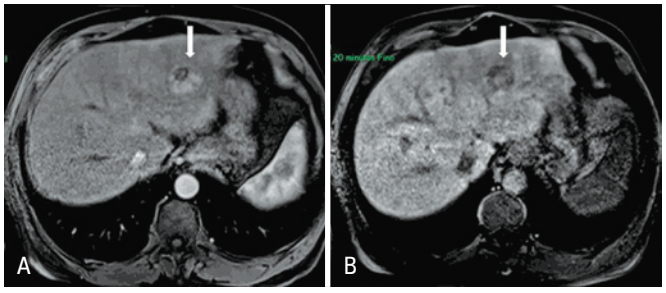

Figure 1. MRI with liver-specific contrast medium in a chronic liver disease patient showing a typical hepatocellular carcinoma on the left lobe. In the arterial phase (A) the lesion is predominantly hypervascular, while in the late hepatobiliary phase it presents a (B) predominant low signal intensity

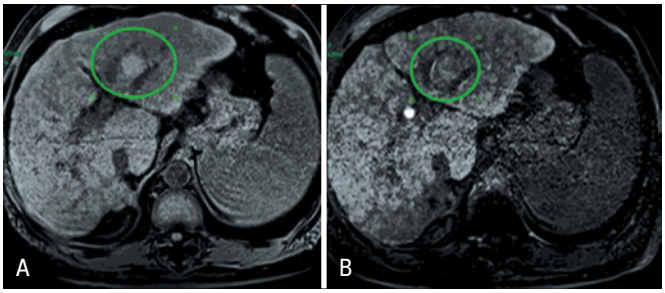

Figure 2. MRI with liver-specific contrast in a chronic liver disease patient showing lesion with characteristics of dysplastic nodule on the left lobe. Lesion shows hyperintensity in pre-contrast phase (A), and iso/hyperintensity in late hepatobiliary phase (B)

low signal intensity in the hepatobiliary phase can be considered as such for therapy planning, because the risk of malignant changes is very high.

HYPERVASCULAR HEPATOCELLULAR CARCINOMA *VERSUS* PSEUDOLESION WITH ARTERIAL ENHANCEMENT

Arterioportal 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).

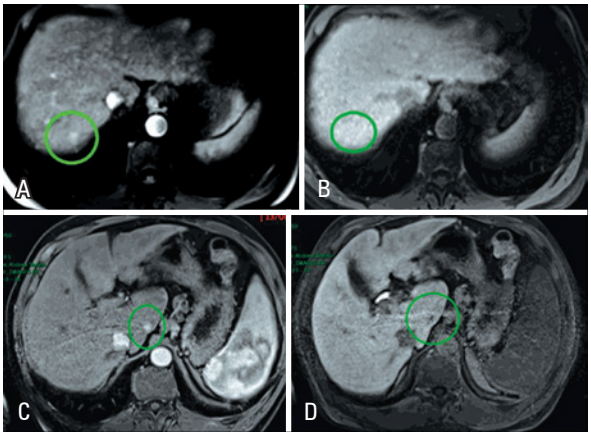

Figure 3. MRIs with liver-specific contrast medium of two chronic liver disease patients. The first patient shows nodular hypervascular focus on segment VII (A), with isointensity to the rest of the parenchyma in late hepatobiliary phase (B), indicating arterioportal shunt. The second patient shows a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

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.

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