

Magnetic resonance of the liver with hepato-specific contrast: initial clinical experience in Brazil

Ressonância magnética do fígado com contraste hepato-específico: experiência clínica inicial no Brasil

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A B S T R A C T

The authors report the initial clinical experience, in a private service in Brazil, with the use of gadoxetic acid, a hepatic-specific magnetic resonance imaging (MRI) contrast medium. This substance, recently approved for commercial use in the country, can be specifically captured by hepatocytes, reaching a peak concentration in about 10-20 minutes after intravenous injection. The main indications for its use in MRI include: diagnosis of hepatocellular carcinoma, detection and treatment planning of liver metastases and the differentiation between focal nodular hyperplasia and hepatocellular adenoma.

Key words: Magnetic resonance imaging. Gadolinium. Contrast media. Carcinoma, hepatocellular. Liver.

INTRODUCTION

Magnetic resonance imaging (MRI) stands out as the method of non-invasive imaging of greater accuracy in both detection and characterization of focal hepatic lesions in cirrhotic and non-cirrhotic patients. This is due in part to better soft tissue contrast inherent to this mode, to the new technologies such as diffusion-weighted images, and especially to the dynamic study of the liver after administration of gadolinium-based contrast media¹.

In the context of MRI of the liver, contrast media can be categorized into hepatic-specific or non-specific². Non-specific contrast means comprise the majority of routinely used substances in MRI, and are distributed over the extracellular spaces, both intra and extra-vascular, regardless of the tissue of interest. They impregnation pattern follows the distribution of blood vessels and capillaries, and is subject to the knowledge of the injection conditions (volume, concentration, injection rate) and hemodynamic parameters for proper interpretation of the findings. For the liver, the dynamic acquisition of images after administration of gadolinium-based non-specific contrast is well established, with arterial, venous (or portal) and late (or balance) phases. Thus, for example, the pattern of impregnation typical of hepatocellular carcinoma (HCC) would be irregular and early mosaic enhancement in the arterial phase, with following washout in the venous

and late phases, with the possibility of pseudocapsule formation.

As for the hepatic-specific contrast media, they are those specifically captured by the liver cells, whether the Kupffer cells or the hepatocytes. The hepatocyte-specific contrast agents are made of gadolinium, with liposoluble properties, while the Kupffer cell-specific substances are generally based on superparamagnetic iron. The gadoxetic acid (Primovist®, Bayer) is the first hepatic-specific contrast medium recently approved for clinical use in Brazil. This paper aims to report the first tests with this substance in a private Radiology service in Brazil, and to advise on key applications and clinical indications.

Mechanism of action and technical aspects

The gadoxetic acid is a contrast medium based on gadolinium, which has an estimated excretion of 50% via the kidney and 50% biliary in healthy patients³. Consequently, a single bolus injection of gadoxetic acid allows routine dynamic three-phase studies of the liver in a first step, followed by hepatobiliary evaluation after an interval of about 10-20 minutes. Another contrast medium with similar features, the dimeglumine gadobenate (MultiHance®, Bracco) also provides this same approach, but it is not yet approved for use in Brazil, and has only 4% of biliary excretion (3), which requires a greater delay for this phase.

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Due to its liposoluble characteristics, gadoteric acid enters into hepatocytes through the cell membrane transporters type OATP1B1 and OATP1B3, and exits through the canalicular ATP-dependent protein related to multidrug resistance (MRP2)⁴. There are also proteins MRP3 and MRP4, allowing efflux of contrast medium back to the liver sinusoids. The knowledge of these biochemical properties has generated several studies based on genetic and protein expression, allowing a better understanding of the in vivo behavior of this contrast medium in various liver injuries.

The MRI exam should be requested as "liver MRI with hepatic-specific contrast" or "liver MRI with hepatobiliary contrast" to differentiate from routine upper abdominal MRI studies. This test lasts about 25-30 minutes and includes the routine pre-contrast series, the dynamic study after gadoteric acid injection, and hepatobiliary phase, all of which are evaluated together. It is not technically permissible to perform the test on MRI devices of open field, of low-field (<1.5 T), much less on devices unable to acquire three-dimensional images of high resolution in fat-suppressed T1.

The gadoteric acid has demonstrated a reasonable tolerability profile, no case of nephrogenic systemic fibrosis being reported related to its use⁵. However, just as with other contrast media based on gadolinium, it is recommended to avoid its use in patients with a creatinine clearance less than 30 ml/min. Furthermore, it is described that the hepatobiliary phase cannot bring relevant information in patients with total bilirubin levels greater than 3.2 mg/dL.

Why use hepatic-specific contrast media in MRI?

Since the gadoteric acid may be specifically absorbed by hepatocytes and excreted into the bile, the contrast medium is a marker of liver tissue normal functioning. Thus, put in a somewhat simplified manner, when there is no gadoteric acid capture in the hepatobiliary phase, it means that there is no viable hepatocytes (eg undifferentiated hepatocellular carcinomas (U-HCC), metastases, hemangiomas) or no bile canaliculi (eg, hepatocellular adenoma). Similarly, lesions which capture the gadoteric acid in the hepatobiliary phase are those in which some level of normal architecture of the hepatobiliary parenchyma remains (eg, focal nodular hyperplasia, regenerative nodules / dysplastic pseudolesions).

From the clinical point of view, the three most common indications for tests with this type of contrast are:

- Diagnosis and staging of HCC in cirrhotic patients.
- Diagnosis and surgical planning of liver metastases.
- Differentiation between focal nodular hyperplasia (FNH) and adenoma.

Clinical experience and practical examples

We performed MRI with acid gadoteric since October 2012, that being the first purchase of the product registered in Brazil. Since then, 15 tests were performed, with the following diagnoses: FNH (n = 3), HCC (n = 4), liver metastases (n = 4), hepatic adenoma (n = 1), hepatic adenomatosis (n = 1), cholangiocarcinoma (n = 1) and transient perfusion abnormalities (n = 1).

According to our observations, the hepatobiliary phase enabled by the gadoteric acid brought diagnostic advantages in that it added objective reliability in the differentiation of hepatocellular adenoma and FNH (Figure 1). As shown in the figure, both such lesions are hypervascular in the arterial phase of the dynamic study and become isointense with the liver in the subsequent phases. When there is no classic scar on the focal nodular hyperplasia, differentiation between the two entities is difficult. With the use gadoteric acid, focal nodular hyperplasia has an enhancement equal or greater than the liver parenchyma's during the hepatobiliary phase, whilst the hepatocellular adenoma does not significantly capture the contrast or exhibits only a peripheral halo⁵.

In the evaluation of liver metastases (Figure 2), the most interesting feature of gadoteric acid is the ability

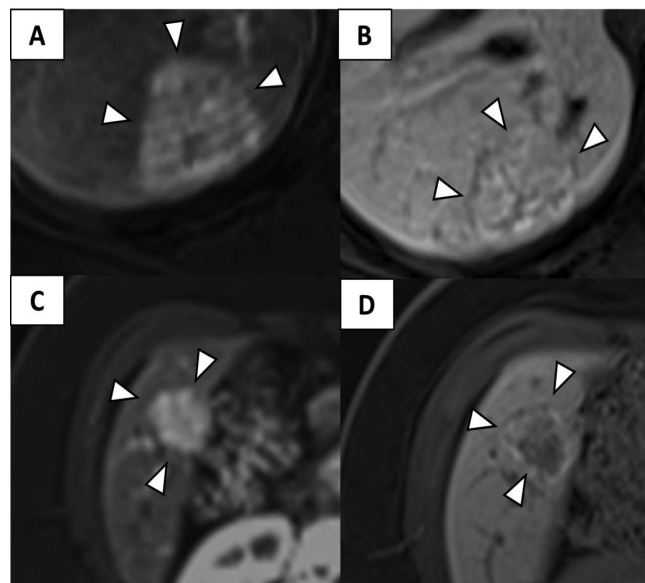


Figure 1 - Utility of acid gadoteric in differentiating FNH and hepatocellular adenoma. Images A and C illustrate hypervascular lesions (arrow-heads) identified in the post-contrast arterial phase in two different patients, of difficult differentiation between FNH and adenoma. Images B and D represent the hepatobiliary phase in both patients. The persistent hepatobiliary enhancement of the B lesion safely allowed the diagnosis of FNH, while the low hepatobiliary uptake (D), with without a peripheral halo, features hepatocellular adenoma.

to detect more lesions in the hepatobiliary phase⁴, with dimensions as small as 0.2 cm, particularly when employing high resolution three-dimensional images in more recent generations devices. In one of the cases evaluated, the patient presented had a prior routine examination suggesting possible surgical indication and the MRI with contrast hepato-specific identified three additional lesions, which changed the treatment plan.

In the context of cirrhotic patients, gadoxetic acid displays good accuracy in differentiating dysplastic nodules from moderately or poorly differentiated HCC nodules³. The latter, no longer having typical hepatocytes and viable hepatobiliary architecture, do not exhibit demonstrable enhancement by gadoxetic acid in the hepatobiliary phase (Figure 3). However, it is known that well-differentiated HCC nodules can maintain a certain degree of enhancement in the hepatobiliary phase.

CONCLUSION

Hepatobiliary contrast media add a new perspective to the management of focal hepatic lesions, and there are several studies on the evaluation of diffuse liver diseases. In our country, only gadoxetic acid is commercially available as yet, and it has been a valuable addition to solving specific diagnostic issues of those lesions.

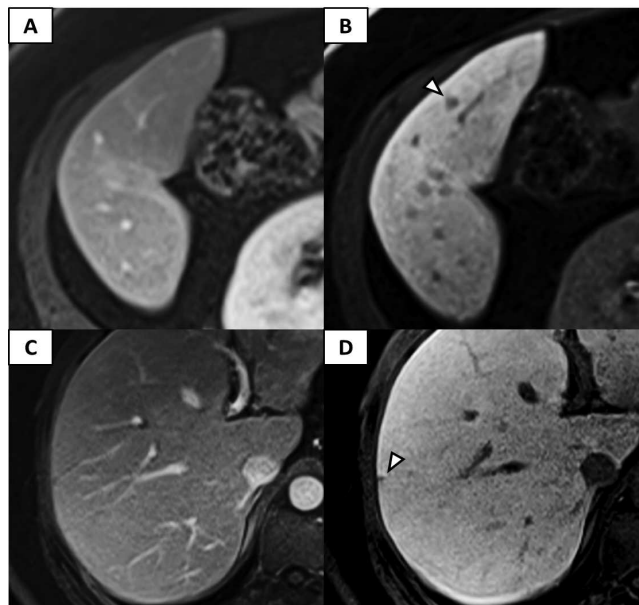


Figure 2 - Value of gadoxetic acid in the detection of liver metastases. The images depict two different patients suffering from colorectal metastases, and candidates for curative resection. The images of the venous phase of the dynamic study (A and C) did not demonstrate lesions in the regions depicted above. However, the hepatobiliary phase (B and D) identified previously unsuspected new metastatic lesions (arrow-heads) with dimensions as small as 0.2 cm. These new findings changed the patients' therapeutic plan.

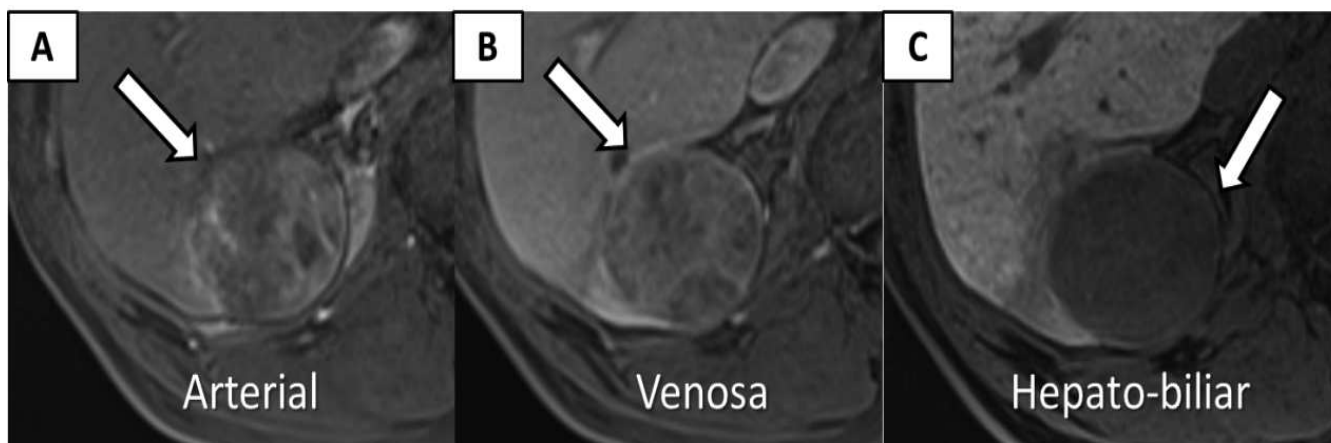


Figure 3 - Typical aspect of HCC in studies with gadoxetic acid, with early and heterogeneous enhancement in the arterial phase (A), some degree of washout in the venous phase (B), and markedly low uptake in the hepatobiliary phase (C). Most times, the latter feature allows the differentiation between regenerative/dysplastic nodules and poorly/moderately differentiated HCC nodules.

R E S U M O

Os autores relatam a experiência clínica inicial em um serviço privado no Brasil do uso do ácido gadoxético como meio de contraste hepato-específico em exames de ressonância magnética (RM). Esta substância, recentemente liberada para uso comercial no país, pode ser especificamente captada pelos hepatócitos, atingindo um pico de concentração em cerca de 10-20 minutos após a administração endovenosa. Dentre as principais indicações para seu uso em exames de RM, figuram: diagnóstico de carcinoma hepatocelular, detecção e planejamento terapêutico de metástases hepáticas, e a diferenciação entre hiperplasia nodular focal e adenoma hepatocelular.

Descritores: Imagem por ressonância magnética. Gadolínio. Meios de contraste. Carcinoma hepatocelular. Fígado.

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