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Gadolinium Dimeglumine as a Contrast Agent for Digital Subtraction Angiography: *in Vitro* Hounsfield Unit Measurement and Clinical Efficacy

Man Deuk Kim[1] and Hyun Kim[2]

[1]Department of Diagnostic Radiology, Bundang CHA General Hospital, College of Medicine, Pochon CHA University, Sungnam-si, Kyonggi-do, Korea;
[2]Department of Diagnostic Radiology, Taejon St.Mary's Hospital, College of Medicine, Catholic University, Taejon-si, Korea.

The purpose of this study was to evaluate the feasibility and safety of using gadolinium-chelates for digital subtraction angiography (DSA) in patients with contraindications to iodinated contrast material, and to assess the clinically effective concentration of gadolinium (Gd).

Gadopentetate dimeglumine and iopromide were used in density measurements. Using 20 mL disposable syringes, serial dilutions of Gd and iopromide with saline were performed. Computed tomography scanning was done and the attenuation of each was recorded as mean Hounsfield units using region of interest analysis. Clinical trials were done in twelve patients with the following types of angiogram or intervention: hemodialysis access, percutaneous biliary drainage, percutaneous nephrostomy, cerebral angiography and transarterial chemoembolization (TACE) in hepatocellular carcinoma. The density of 1 : 1 diluted Gd was nearly equal to that of 1 : 4 dilution of iopromide, and that of pure Gd was similar to or less than that of 1 : 1 dilution of iopromide. Serum creatinine level was not elevated in any of the patients.

Gd is a safe alternative agent in patients with contraindications to iodinated contrast materials. Pure Gd without dilution is the most clinically useful concentration.

Key Words: Gadolinium, hounsfield unit, DSA

INTRODUCTION

Contrast induced renal failure in patients with renal insufficiency has been reported to occur in 10 - 50% of patients receiving iodinated contrast material.[1] Besides, use of iodinated contrast material is limited in patients with a history of significant allergy to iodinated contrast material.

Gadolinium (Gd) has a higher atomic number than iodine and is more radiopaque than iodine at the same concentration. Furthermore, Gd has little nephrotoxicity due to good renal tolerance in patients with pre-existing renal impairment.[2] The purpose of this study was to evaluate the feasibility and safety of using Gd-chelates for digital subtraction angiography (DSA) in patients with contraindications to iodinated contrast material and in volunteers, and to assess the clinically effective concentration of Gd.

MATERIALS AND METHODS

Density measurements

Gadopentetate dimeglumine (0.5 mol/L, Magnevist, Schering, Berlin, Germany) and iopromide (Ultravist 300, Schering, Berlin, Germany) were used in density measurements. Using 20 mL disposable syringes, serial dilutions of Gd and iopromide with saline were performed. Computed tomography (CT) scanning (Somatom plus 4, Siemens Medical Systems, Forchheim, Germany) with 10 mm thickness, axial sections was done and the attenuation of each scan was recorded as mean Hounsfield units (HU) using region of in-

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Reprint address: requests to Dr. Man Deuk Kim, Department of Diagnostic Radiology, Bundang CHA General Hospital, College of Medicine, Pochon CHA University, 351 Yatap-dong, Bundang-gu, Sungnam-si, Kyonggi-do, Korea. Tel: 82-31-780-5382, Fax: 82-31-780-5381, E-mail: mdkim@cha.ac.kr

terest (ROI) analysis. Three ROI per section were measured on four continuous sections, and a total of 12 ROI were assessed.

Clinical applications

Clinical trials were done in twelve patients: hemodialysis access in the forearm (n=4), percutaneous transhepatic biliary drainage (n=3), percutaneous nephrostomy (n=3), cerebral angiography (n=1) and transarterial chemoembolization (TACE) in hepatocellular carcinoma (n=1). Among the patients, four had renal dysfunction and four had a history of hypersensitivity reaction.

The serum creatinine levels were measured prior to the procedure and 24 and 48 hours after the procedure. Total dosage of Gd used was 20-40 cc.

RESULTS

In iopromide, HU of pure solution was 3070.5 and that of 1:1 dilution was 2777.9, a 9.5% decrease in density (Table 1). In case of Gd, HU of pure solution was 2679.7 and that of 1:1 diluted Gd was 1435.2, a 46.4% decrease in density. The density of 1:1 diluted Gd was nearly equal to that of 1:4 dilution of iopromide and that of pure Gd was similar to or less than that of 1:1 dilution of iopromide. Therefore, pure Gd without dilution seem to be the most effective choice. Serum creatinine level was not elevated in any of the patients. In clinical trials, only the Gd chelates were used as contrast agent in eleven exams and 8 mL of iodinated contrast was additionally used as well as Gd in cerebral angiography. In arteriovenous fistulogram of the forearm after angioplasty, the density of Gd was suddenly decreased, due to the dilution effect of increased blood flow (Fig. 1). Percutaneous nephrostomy (Fig. 2) and cholangiogram (Fig. 3) for percutaneous transhepatic biliary drainage were done adequately using Gd. Routine cerebral angiography was performed in a patient suspected of moya-moya disease in magnetic resonance imaging (MRI). However, whereas the fine moya-moya vessels were poorly demonstrated using Gd, 8 mL of iopromide was required to repeat the anteroposterior view of the right internal carotid angiogram (Fig. 4).

Hepatic angiogram was done in a patient who had been treated with TACE for hepatocellular carcinoma eight months previously (Fig. 5). The patient had experienced acute rejection following a kidney transplantation three years previously. Due to the elevated serum creatinine level, angiography was performed using Gd. The angiography was adequate for the diagnosis of a newly developed hepatoma and for subsequent TACE.

Table 1. HU Measurements of Serial Diluted Gadolinium and Iopromide

	Gadolinium	Iopromide
Pure	2679.7	3070.5
1:1	1435.2	2777.9
2:1	1028.6	1983.0
4:1	642.2	1486.8
10:1	327.9	767.6
50:1	92.0	216.8
100:1	54.8	134.4

DISCUSSION

Contrast material-induced acute renal failure, defined as a sudden rise in serum creatinine level of greater than 0.5 mg/dL (44 umol/L) within 48 hours, is an important complication of angiography. Iodine contrast agents have a known risk of renal toxicity when renal function is normal, and this risk increases when renal insufficiency is present. The frequency of iodinated contrast material-induced acute renal failure after peripheral angiography may be as high as 41% in patients with serum creatinine levels greater than 1.5 mg/dL.[3] Diabetes and underlying renal insufficiency have been consistently identified as risk factors for iodinated contrast-induced nephropathy.[4] Hyperthyroidism is also a contraindication for administration of iodinated contrast agents. Many patients suffer from multifocal autonomic adenomas that might be triggered by the excessive load of iodine, which may lead to thyrotoxicosis.[5] A nonnephrotoxic contrast agent is needed that can be used during angiography in patients with azotemia. In patients with renal insufficiency

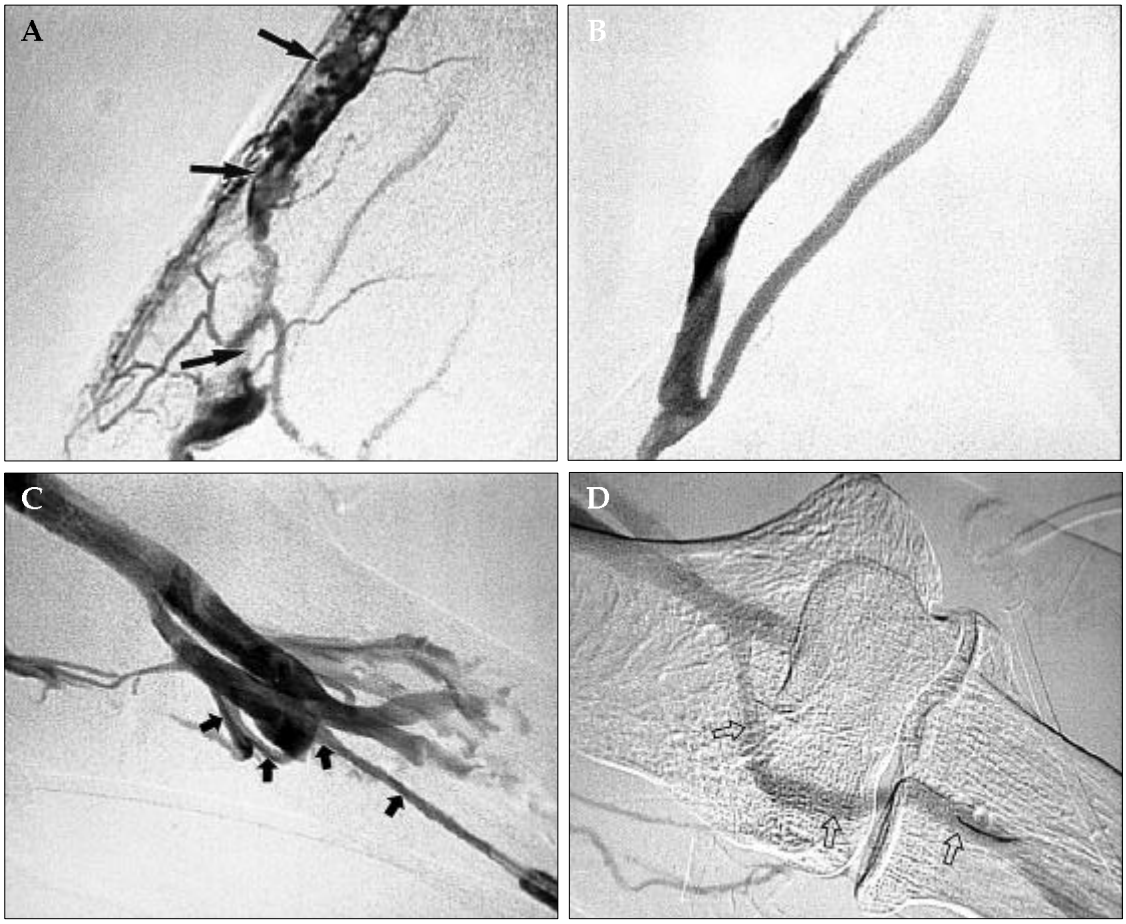

Fig. 1. Angioplasty of arteriovenous fistula in the forearm in 44 year-old male with a history of hypersensitivity reaction to iodinated contrast material. (A) In fistulogram using Gd, stenosis and thrombosis of venous limb (arrows) are adequately demonstrated. (B) Fistulogram after balloon dilatation shows good restoration of blood flow. (C) Stenosis of draining vein (arrows) is also seen. (D) On follow up angiogram using Gd after successful angioplasty, sudden decrease of density (arrows) is demonstrated due to the dilution effect of increased blood flow.

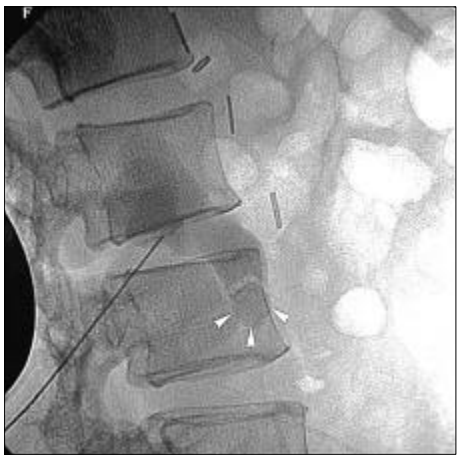

Fig. 2. Pyelogram for percutaneous nephrostomy. Right ureter stone (arrowheads) with obstructive hydronephrosis is well visualized using Gd.

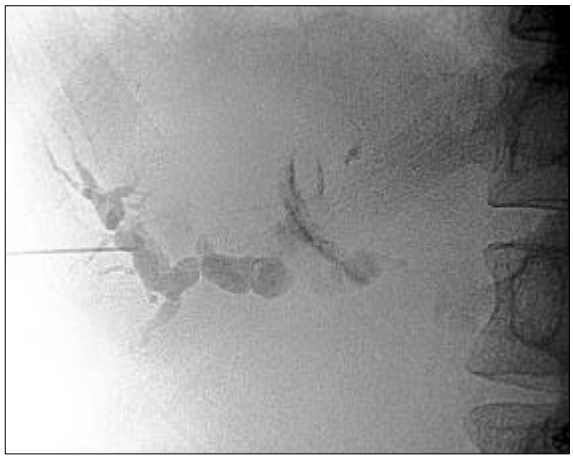

Fig. 3. A 53-year-old male with obstructive jaundice. Cholangiogram for percutaneous transhepatic biliary drainage was demonstrated using Gd.

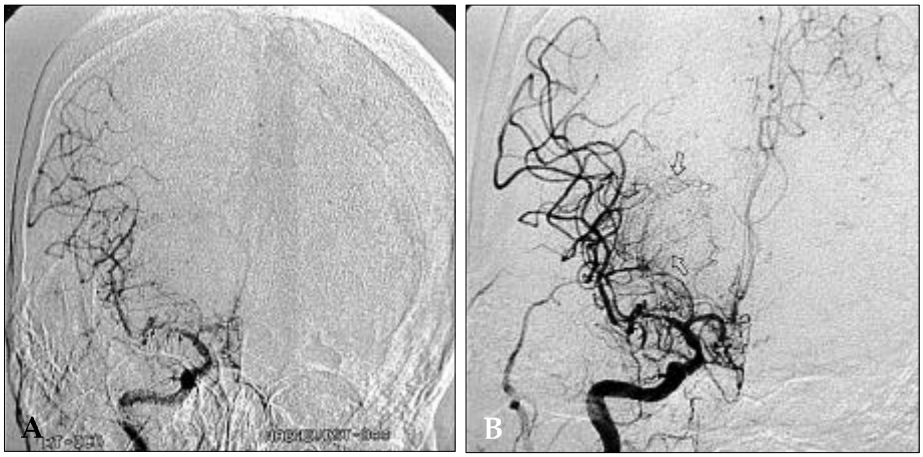

Fig. 4. A 61-year-old female; moya-moya disease and renal insufficiency (Serum creatinine 3.0 mg/dl) (A) Right internal carotid arteriogram using Gd shows severe stenosis of the middle cerebral artery(arrows), but fine moya moya vessels are only faintly visualized. (B) When iopromide is used, moya-moya vessels (arrowheads) are better demonstrated.

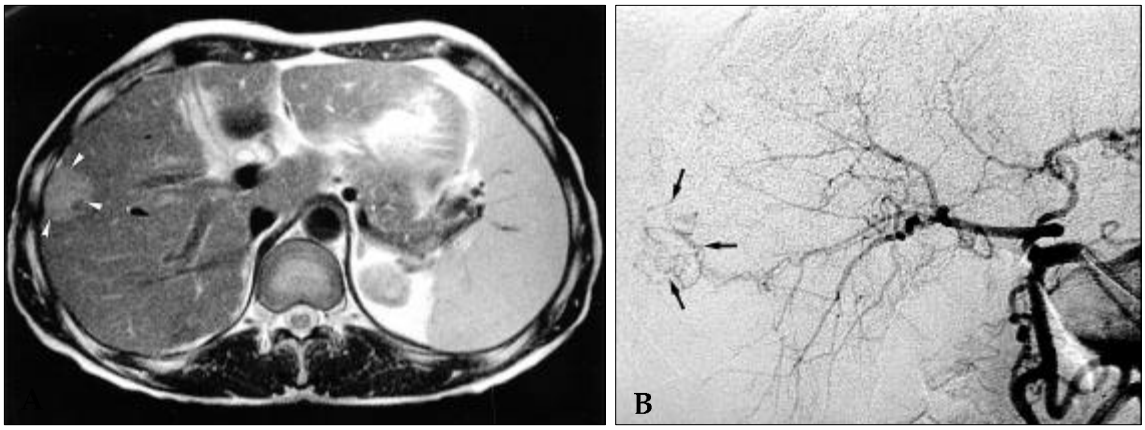

Fig. 5. A 53-year-old male who had received kidney transplantation was diagnosed with newly developed hepatocellular carcinoma and renal insufficiency. (A) On T2 weighted axial image, increased signal intensity of hepatocellular carcinoma (arrowheads), as proven by biopsy, is seen on the right lobe of the liver. (B) Hepatic artery angiogram using Gd shows tumor staining (arrows) of hepatoma. Chemoembolization was done.

(serum creatinine level, greater or equal to 1.5 mg/dL, 133 umol/L), an alternative contrast agent with a low risk of contrast agent-induced acute renal failure is desirable. Patients with pre-existing chronic renal failure have shown good renal tolerance for Gd.[2] High-dose gadopentetate dimeglumine (up to 0.4 mmol/kg) has been shown to be safe and well tolerated in patients with normal or abnormal renal function.[6] Carbon dioxide (CO_2) has been used as an alternative contrast agent to iodine in DSA. However, complications of transient colonic ischemia, rhabdomyolysis, massive intestinal infarction, and death from a suspected vapor lock phenomenon have been reported.[7,8] Use of Gd-based contrast agents is not entirely without risk. Adverse reactions, including true anaphylaxis, are rare but do occur.[9] One case of acute renal failure after arteriography with 80 mL of gadodiamide (0.44 mmol/kg body weight) has been reported.[10] Cross sensitivity in patients with prior anaphylaxis to iodinated contrast agents does not appear to be a problem.

Theoretically, Gd-based contrast agents should work well as radiologic contrast agents. Gadopentetate dimeglumine has an atomic number of 64 and a k edge of 52 keV, compared with 53 and 33 keV, respectively, for iodine. *In vitro* experimental findings have shown that above a mean peak setting of 72 kVp ± 6, image contrast is better with Gd-based contrast agents than with iodinated agents.[11] Below this kilovolt peak setting, iodine provides image contrast superior to

that with Gd-based contrast agents. Despite the theoretically favorable x-ray imaging properties of Gd-based contrast agents, the actual vascular enhancement observed during DSA is weaker than that observed with iodinated contrast agents because of the relatively low concentration of Gd in currently available MRI contrast agents. Further prospective trials are mandatory to find evidence for nonnephrotoxicity and confirms the safety of application at higher Gd concentrations. The use of very expensive Gd-based contrast agents may be justified in patients with azotemia when its cost is compared with that of treating iodinated contrast induced acute renal failure. Image contrast would seem to be generally adequate when Gd-DTPA is administered locally. We recommend pure solution of Gd, without dilution, as the attenuation graph shows that HU of 1 : 1 diluted Gd was less than that of 4 : 1 dilution of iopromide, and as sudden decrease of density due to dilution effect occurred. When dilution occurs, Gd-agents may be poorly visible. In cerebral angiography using Gd, it was more difficult to evaluate fine vascular structures such as moyamoya vessels, compared with images obtained by iodine contrast agent. Gd was feasible in repeat TACE, when the anatomy or variation of hepatic artery had been revealed. In our case of recurrent hepatoma, only hepatic arteriogram was obtained, because of poor visual conspicuity of the large blood flow of celiac and superior mesenteric angiography. Therefore, a prior review of hepatic artery anatomy or variation was required using previous hepatic angiogram performed by iodinated contrast agent. We concluded that Gd is a safe alternative agent in patients with contraindications to iodinated contrast materials, like renal insufficiency or hypersensitivity. However, further studies with large population sizes should be performed. For local use, pure Gd without dilution provides the most beneficial clinical effect.

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