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Lack of nephrotoxicity of gadopentetate dimeglumine-enhanced non-vascular MRI and MRI without contrast agent in patients at high-risk for acute kidney injury

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Background: Gadolinium chelates (GCs) have been traditionally considered as non-nephrotoxic magnetic resonance imaging (MRI) contrast materials. However, it has been suggested in some recent articles that GCs may have a nephrotoxic potential, but most of these reports are retrospective. However, the evaluated contrast agents, their doses, and the tests used to determine the kidney function were not consistent across studies. We aimed to investigate the effect of magnetic field and an MRI contrast agent, gadopentetate dimeglumine (GD), on renal functions in patients at high risk for acute kidney injury (AKI).

Material/Methods: We designed a prospective case-control study with 2 age- and sex-matched groups of patients at high-risk for AKI (n=72 for each group). Patients in Group 1 received a fixed dose of (0.2 mmol/kg) GD-enhanced non-vascular MRI and patients in Group 2 received MRI without GD. Before the MRI and at 6, 24, 72, and 168 hours after the MRI, biochemical tests, estimated glomerular filtration rate (eGFR), albumin/creatinine ratio in spot urine, and early AKI biomarkers (cystatin C, N-Acetyl-Glucosaminidase [NAG], Neutrophil gelatinase-associated lipocalin [NGAL]) were measured.

Results: Serum creatinine, albumin/creatinine ratio, and eGFR were not different between Group 1 and 2 ($p>0.05$). There were no significant changes in renal function tests and AKI biomarkers ($\Delta_{\text{serum creatinine}}$, $\Delta_{\text{albumin/creatinine ratio}}$, Δ_{GFR}, $\Delta_{\text{cystatin c}}$, Δ_{NAG}, and Δ_{NGAL}) for either groups 6, 24, 72, and 168 hours after the procedures ($p>0.05$).

Conclusions: MRI without contrast agent and non-vascular contrast-enhanced (GD, 0.2 mmol/kg) MRI are not nephrotoxic procedures for patients at high risk for AKI.

Key words: MRI • gadopentetate dimeglumine • contrast nephropathy • acute kidney injury • NAG • NGAL

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Background

Imaging procedures with iodinated radiological contrast agents (ICAs) remain an important cause of acute kidney injury (AKI) for hospitalized patients. The pathogenesis of contrast-induced nephropathy (CIN) is still controversial, and is likely to be multifactorial. Some risk factors for CIN have been well defined: chronic renal insufficiency, older age, concomitant use of other nephrotoxic agents, hypotension, diabetes mellitus, and congestive heart failure are the main risk factors for the development of CIN. The risk of development of CIN has been shown to rise strikingly with the number of risk factors present [1].

Gadolinium chelates (GCs) have been traditionally used as a non-nephrotoxic alternative to ICAs for digital subtraction angiography (DSA), especially in patients at high risk for AKI. However, its use has been questioned on the basis of reports of nephrotoxicity, even in non-vascular MRI [2,3]. Many clinical studies and some case reports of GCs-associated AKI have been published [4]. Nevertheless, the quality of these studies is poor, and the evidence of nephrotoxicity due to GCs is conflicting.

A recent study suggests that *in vivo* release of gadolinium ion through transmetallation and its retention in tissues are closely related with the genesis of some GCs-associated tissue toxicity [5]. However, the specific effects of GCs on different tissues, including heart, kidney or liver, remain undefined. We aimed to investigate the effect of magnetic field and an MRI contrast agent, gadopentetate dimeglumine (GD), on renal functions in patients at high risk for AKI. In addition to conventional tests (serum creatinine, glomerular filtration rate [GFR], albumin/creatinine ratio in spot urine), early novel AKI biomarkers (cystatin C, N-Acetyl-Glucosaminidase [NAG], neutrophil gelatinase-associated lipocalin [NGAL]) were also used to assess the renal functions in our subjects.

Material and Methods

We designed a prospective case-control study. Two age- and sex-matched groups (n=72 for each group) of hospitalized patients at high risk for AKI were included into the study. All patients in both groups had 1 or more definite risk factors for AKI (advanced age [>75 years], diabetes mellitus, chronic kidney disease, congestive heart failure, using other nephrotoxins, and hypotension). Data collection and analysis of this determination were approved by the Human Research Ethics Committee (17.04.2009 date and 2009/71 number) of our institution with waiving of the need for informed consent.

Patients with neoplastic diseases, acute or chronic systemic inflammatory conditions (vasculitic syndromes, infectious diseases), AKI, and hyperuricemia were excluded.

We used the Acute Kidney Injury Network (AKIN) diagnostic criteria for CIN. AKIN suggested 2 separate CIN endpoints using both absolute and relative serum creatinine changes [6]. Their proposed diagnostic criteria for AKI [7] included an absolute increase in serum creatinine level of ≥0.3 mg/dl (26.4 μmol/l), or an increase in serum creatinine level of ≥50% (1.5-fold increase from baseline), or a reduction in urine output (documented oliguria of <0.5 ml/kg/h for >6 h) within 48 h. Estimated GFR was measured by the Modification of Diet in Renal Disease (MDRD) equation.

Informed consent was obtained from all patients, and the study protocol was approved by the institute's ethics committee on human research. Contrast (Magnevist® [(Berlex Lab., Wayne, NJ], brand of gadopentetate dimeglumine, 0.2 mmol/kg)-enhanced MRI was performed for lumbar disc herniation in 53 and 62 patients in Group 1 and Group 2, respectively, and evaluation of the patients' symptoms after laminectomy or diskectomy for lumbar disc herniation in 19 and 10 patients in Group 1 and Group 2, respectively. GD was administered by slow intravenous injection. No preventive method for CIN was performed. All study subjects were observed for 1 week after the procedures.

Systolic and diastolic blood pressure was measured before and after the procedures by a standardized automated device (Omron M6 Comfort, Matsusaka, Mie, Japan). Subjects were defined as hypotensive if they had permanent systolic blood pressure less than 100 mmHg,.

Serum creatinine, albumin, uric acid, serum electrolytes, total cholesterol, low-density lipoprotein, triglyceride, liver enzymes, fasting blood glucose, hemoglobin A1C, and C-reactive protein (CRP) levels were measured before the procedures in all subjects. Serum creatinine, CRP, eGFR, serum cystatin C, NAG, and NGAL levels were measured at baseline, and at 6, 24, 72, and 168 h after the procedures and albumin/creatinine ratio was measured in morning spot urine at baseline and 168 h after the procedure.

Serum cystatin C concentration was measured by immunonephelometric assay, and was considered normal up to a maximal value of 1.50 mg/dl. Serum levels of NGAL were measured by a research ELISA (cat. no. KIT 037, BioPorto Diagnostics, Denmark). Urine NAG levels were measured with spectrophotometric method using a commercial NAG diagnostic kit (cat. no. DZ062A) (Diazyme Lab, CA, USA) (Cobas 501 Roche Diagnostics, Manheim, Germany).

MRI procedure

MRI of the knees was performed with a 1.5-T MR scanner (1.5 Intera, Philips, Best, The Netherlands). MR examination took

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Table 1. Base-line demographic and laboratory parameters in groups.

Parameters	Group 1 (n=72)	Group 2 (n=72)	p
Age (years)	65.5±14.4	64.2±11.1	NS
Sex (Female/Male)	42/30	39/33	NS
Haemoglobin (gr/dl)	12.8±1.7	12.4±1.4	NS
Serum creatinine (mg/dl)	1.82±0.25	1.77±0.19	NS
Fasting blood glucose (mg/dl)	124.7±34.1	132.1±12.9	NS
HbA1c (%)	7.2±2.1	7.4±0.2	NS
Albumin (g/dl)	4.3±0.3	4.5±0.1	NS
Total cholesterol (mg/dl)	196.9±25.2	187.5±33.1	NS
Low-density lipoprotein (mg/dl)	105.6±21.3	102.5±14.1	NS
Triglyceride (mg/dl)	152,2±23.0	134.1±12.1	NS
Uric acid (mg/dl)	5.9±1.6	5.6±1.4	NS
C-reactive protein (mg/l)	3,5±1.1	3.2±0.4	NS
GFR (CKD-EPI) (ml/dk/1.73 m^2)	36.4±7.1	38.8±6.7	NS
$[A/Cre]_{spot\ urine}$ (mg/mg)	198.9±59.5	180.3±72.7	NS

GFR – glomerular filtration rate; MDRD – "modification of diet in renal disease" formula; A/Cre – microalbumin/creatinine ratio in morning spot urine; NS – not significiant.

about 15–20 min per patient. Pulse sequences consisted of: sagittal proton density-weighted sequence (TR 2618 ms, TE 15 ms, slice thickness 4 mm, slice gap of 0.30, matrix 256×256); sagittal T2-weighted turbo spin-echo (TR 2618 ms, TE 100 ms, slice thickness 4 mm, slice gap of 0.30, matrix 256×256); coronal short Tau inversion recovery (STIR) (TR 1689 ms, TE 15 ms, TI 160 ms, slice thickness 3 mm, slice gap of 0.30, inversion time=160 ms, matrix 512×512); sagittal fat-suppressed, 3-dimensional, spoiled gradient-echo sequence (TR 20 ms, TE 7.827 ms, slice thickness 1.5 mm, no intersection gap, matrix 512×512); and axial T2-weighted turbo spin-echo (TR 6140 ms, TE 100 ms, slice thickness 3 mm, slice gap of 0.30, matrix 512×512). The images were acquired with a field of view of 17 cm (proton density-weighted sequence, sagittal T2 turbo spin-echo sequence) and 15 cm (all other sequences).

MRI scans of the lumbosacral region were obtained with a GE 1.5-T unit (1.5 Intera, Philips, Best, The Netherlands) and using a spine array coil. The following spin-echo sequences were used: Axial localizer (spoiled gradient), sagittal T1 (TE minimum full/TR 400), sagittal T2 (TE 100/TR 4000), sagittal proton density (TE 10–20/ TR 2000), axial T1 (TE minimum full/TR 400) (thickness 4 mm/spacing 0.4 mm, matrix 512×512, FOV 26 cm). Magnevist® [(Berlex Lab., Wayne, NJ], brand of gadopentetate dimeglumine, 0.2 mmol/kg, were administered in all procedures.

Statistical analysis

Descriptive statistics are shown as mean ± standard deviation for continuous variables. Results for Group 1 and 2 were compared by *t* test for quantitative data and Fisher's exact test for proportions. Repeated measures ANOVA was used for the comparison of changes in serum creatinine, GFR, albumin/creatinine ratio, cystatin C, NAG, and NGAL for both groups. Partial correlation analysis was used to control for confounding factors in correlation analysis. Statistical analysis was performed with the MedCalc computer program and statistical significance was set at $p<0.05$.

Pre-study power analysis was done with the goal of establishing the risk of AKI – the difference between the 2 groups in the proportion of patients reaching the primary endpoint would be <0.10 with 95% confidence. For the power analysis, it was estimated that 40% of the both groups group would reach the endpoint. It was determined that 154 patients per group would ensure adequate precision but we were not able to include this number of subjects.

Results

Demographic characteristics and laboratory parameters in both groups are shown in Table 1. The types and number of risk factors

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Table 2. The type and number of risk factor for acute kidney injury in groups.

Risk Factors	Group 1 (n=72)	Group 2 (n=72)	p
Type 2 Diabetes Mellitus (n)	48	51	NS
Hypotension (n)	14	12	NS
Nephrotoxin exposure* (n)	54	50	NS
Peripheric artery disease (n)	7	9	NS
Congestive heart failure (n)	32	28	NS
Total number of risk factors (n)			
1	11	14	NS
2	42	44	NS
≥3	19	14	<0.05

* Non-steroidal antiinflammatory drugs for pain management; NS – not significiant.

for AKI in both groups are shown in Table 2, and were not different significantly between groups, except for patients having >3 AKI risk factors ($p<0.05$). Baseline albumin/creatinine ratio in spot urine and eGFR were not different between groups ($p>0.05$).

We did not observe any acute adverse effects related with the procedures and we did not detect AKI by conventional or early novel AKI biomarkers in either group. There were no significant changes in renal function tests ($\Delta_{\text{serum creatinine}}$, $\Delta_{\text{albumin/creatinine ratio}}$, Δ_{GFR}, $\Delta_{\text{cystatin C}}$, Δ_{NAG}, and Δ_{NGAL}) in either group 6, 24, 72, and 168 h after the procedures ($p>0.05$) (Table 3). Neither the type nor the number of risk factors determined the tests for renal function assessments after the procedures in either group ($p>0.05$).

After 2 years of observation, nephrogenic systemic sclerosis was not observed in our subjects, even in patients with chronic renal failure.

Discussion

GCs have significantly lower viscosity and are used at significantly lower volumes (4 to 11 times less than ICAs), making them potentially less nephrotoxic. While GCs were initially thought to be a safe alternative to ICAs for patients with chronic renal insufficiency, many clinical studies and case reports of gadolinium-associated AKI have now been recorded, particularly in patients with underlying renal insufficiency. We did not detect AKI, even by early AKI biomarkers, in our patients at high risk for AKI who underwent to MRI procedures with or without contrast agent.

Elmståhl et al. demonstrated that the histomorphological changes caused by gadolinium are similar to those caused by ICMs and are not related with the dose of contrast material in ischemic porcine kidneys [8]. Furthermore, the same authors have also demonstrated that ICM (iohexol) molecules were less nephrotoxic than the GDs (gadopentetate and gadodiamide) in ischemic porcine kidneys [9].

In humans, early studies revealed that GCs are relatively safe molecules in healthy people [10] and in patients with kidney disease [11], but recent studies have suggested that GCs exhibit variable degrees of nephrotoxicity. Nevertheless, the quality of these studies is poor and evidence for the nephrotoxicity of gadolinium-based contrast agents is conflicting. Furthermore, many of these studies are retrospective [12–14]. Many studies have failed to show clear risk factors [13,14]. The types and doses of GCs evaluated in these studies are not homogenous [13–15]. The GCs are classified into 4 main categories on the basis of their biochemical structure and their electrical charge. The various properties of the chelates have implications for possible toxicity and the risk for liberation of free ionic form (Gd^{3+}) from its chelate [16]; therefore, different types of GCs may have a different toxicity potential. For instance, gadodiamide was found to be responsible for nephrotoxicity in some studies, but others did not show this relation [17]. However, a prospective randomized controlled study with a small sample size showed that gadobutrol has no benefit over ICA-based (iohexol) angiography in patients with severely impaired renal function [18]. In the present study, the same agent (GD) at the same dose (0.2 mmol/kg) was used in all study subjects.

Serum creatinine has been used for the assessment of renal function in many of these studies [12–14]. Unfortunately, serum creatinine is a poor and late marker for AKI. Creatinine production varies among individuals based on dietary intake, body habitus, sex, and race. In addition limitations in ability of

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Table 3. Changing in tests for renal function in groups after the MRI procedures.

Parameter	Group 1	Group 2	p
Δ[serum creatinine]			
0–6 h	0.010±0.002	0.012±0.007	NS
6–24 h	–0.02±0.002	0.01±0.009	NS
24–72 h	0.016±0.008	0.017±0.005	NS
0–168 h	0.022±0.004	0.020±0.009	NS
Δ[GFR*]			
0–6 h	–2.2±1.3	–3.1±2.1	NS
6–24 h	1.4±1.2	1.2±0.6	NS
24–72 h	–1.6±1.1	–2.0±1.9	NS
0–168 h	–1.7±0.1.0	–1.9±1.4	NS
Δ[A/cre**]			
0–6 h	3.4±2.1	4.1±3.5	NS
6–24 h	2.1±1.3	2.9±2.2	NS
24–72 h	1.3±2.1	1.6±1.4	NS
0–168 h	2.2±1.5	2.9±3.1	NS
Δ[Cystatine C]			
0–6 h	0.019±0.001	0.020±0.007	NS
6–24 h	0.021±0.004	0.023±0.009	NS
24–72 h	0.020±0.008	0.021±0.005	NS
0–168 h	0.020±0.004	0.022±0.009	NS
Δ[NAG#]			
0–6 h	0.012±0.002	0.010±0.007	NS
6–24 h	–0.014±0.002	0.014±0.009	NS
24–72 h	0.011±0.008	0.012±0.005	NS
0–168 h	0.014±0.004	0.012±0.009	NS
Δ[NGAL##]			
0–6 h	2.4±1.2	2.2±3.5	NS
6–24 h	2.2±1.0	2.5±2.2	NS
24–72 h	2.1±1.7	1.9±1.4	NS
0–168 h	2.2±1.5	2.2±1.1	NS

* GFR – glomerular filtration rate; ** A/cre – microalbumin/creatinine ratio in spot urine; # NAG – N-acetyl glucosaminidase; ## NAGL – Neutrphyl gelatinase-associated lipocalin; NS – not significiant.

serum creatinine concentration to reflect changes in GFR, due to compensatory hypertrophy and hyperfiltration of unaffected glomeruli in cases of progressive glomerular loss, levels of both creatinine and GFR may not necessarily reflect the underlying renal injury. In recent years, a number of novel and predictive biomarkers such as kidney injury molecule-1, NGAL, and cystatin C have been developed, which provide earlier and more specific detection of AKI. In a recent study, while diagnosis of

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AKI with serum creatinine was only possible 1–3 days after cardiopulmonary bypass, serum or urine NGAL rose 20-fold within 2 h after cardiopulmonary bypass [19]. Cystatin C measurement allows earlier detection of AKI as compared to serum creatinine measurement [20]. When compared with NGAL (2–4 h), cystatin C seems to rise later (8–24 h) in AKI [21]. A combination of 2 or 3 biomarkers enhanced the sensitivity of early detection of AKI when compared with individual biomarkers [22]. Besides conventional markers (GFR, microalbumin/creatinine ratio, and serum creatinine), we also used the more specific and early markers for AKI to assess the kidney functions throughout the study. Thus, we conclude that our results were highly reliable.

Direct tubular toxicity, renal ischemia, hemodynamic changes, hyperosmolality, oxidative stress, and patient characteristics (e.g., co-morbidities, pre-procedural glucose levels) have been implicated in the pathogenesis of CIN, but their respective roles remain unclear in GCs-associated AKI [23–26]. Recent reports have shown that GCs cause rat cortical neurotoxicity by inducing intracellular oxidative stress [27], but we demonstrated that magnetic field and gadopentetate dimeglumine (Magnevist®) do not change the oxidant or antioxidant status at a dose of 0.2 mmol/kg [28]. Chien et al. demonstrated that septic condition is a risk factor for GCs-related AKI [29]. In the present study, none of our patients had a septic condition.

The main limitation of the present study is the small size of the study population. For the power analysis, because the results from the both groups were very similar, we estimated that 40% of both groups would reach the endpoint; therefore, we determined that 154 patients per group would ensure adequate precision. Unfortunately, we were unable to enroll this number of subjects.

Conclusions

Non-vascular MRI with GD used at a dose of 0.2 mmol/kg and MRI without contrast agent are not nephrotoxic procedures in patients at high risk for AKI. Furthermore, neither the type nor the number of risk factors for AKI determines the tests for renal function assessments after these procedures. Similar studies should be conducted with prospective cohorts including large numbers of participants.

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