CLINICAL STUDY

Safety of Older Generations of Gadolinium in Mild-to-Moderate Renal Failure

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Abstract

Nephrogenic systemic fibrosis (NSF) is a rare disease that is mostly reported in patients with chronic kidney disease (CKD) who have received gadolinium as a contrast in imaging techniques. The exact pathogenetic role of renal failure or gadolinium is not known. The aim of this study is to show whether mild-to-moderate renal failure is a risk for NSF as it is described in severe renal failure. In this cross-sectional study, we enrolled 164 patients with serum creatinine levels >1.5 mg/dL who were in different stages of CKD and had received gadolinium (gadopentetate). The average lag time between the gadolinium administration and the study was 4 months. The most prevalent skin symptom was itching (19%) and the least frequent was induration and papules (<1%). At the follow-up, all skin lesions were relieved. No patients had characteristic lesions of NSF. Twenty-five percent of patients had acute kidney injury at the time of gadolinium exposure. No patients had liver disease and only five were receiving erythropoietin. None of our patients were taking immunosuppressive agents, but all of them suffered from cardiovascular diseases. We conclude that in patients with mild-to-moderate renal failure, it seems that gadolinium is associated with no or very low risk for NSF. We did not find any NSF in patients with severe renal failure. However, because of the rarity of NSF, the low number of such patients in the study, and the high mortality, the use of gadolinium in these patients should be avoided.

Keywords: nephrogenic systemic fibrosis, chronic kidney disease, gadolinium, magnetic resonance angiography, acute kidney injury

INTRODUCTION

Nephrogenic systemic fibrosis (NSF) is a rare, but potentially fatal disease whose pathophysiological nature remains unclear. This disorder was reported for the first time in 1997 in dialysis patients with skin lesions that looked like scleromyxedema.1 In 2000, the characteristic lesions of NSF were described and it was realized that a new disease had been added to the medical literature. In 2001, the nomenclature of nephrogenic fibrosing dermopathy was introduced and finally NSF was designated to show the systemic nature of the disorder.2 In recent years, with an increasing number of cases of NSF, physicians in different specialties have been attracted to this debilitating disease. Although there were different hypotheses about the mechanisms of the disease, renal failure was the only known factor for the development of NSF up to 2006.

Since 2006, a link between NSF and gadolinium-based contrast agents (GBCAs) has been established.3–8 Although the pathogenic role of GBCAs is not well known, it has been suggested that gadolinium causes NSF via a transmetallation mechanism.9 During this process, gadolinium is replaced with other metal ions in the chelate, and the free gadolinium is shown to be highly toxic for different tissues.10 The suspect ions that replace gadolinium are zinc, copper, iron, and calcium. The time that gadolinium chelate remains in the body is crucial for the transmetallation process. Accordingly, patients with renal failure, especially end-stage renal disease (ESRD), who are not able to disperse gadolinium, are at a higher risk for NSF.10 In addition, the instability of gadolinium chelate is another factor for determining which patients will develop NSF. Today, NSF is commonly reported in patients with severe renal disease...
who are taking gadolinium. The odd ratio of NSF in patients who are exposed to gadolinium is 20-fold higher than in those without exposure. There is also a relationship between the cumulative dose of gadolinium and the NSF development. There are anecdotal case reports of patients with NSF without any history of gadolinium exposure. In most patients, NSF appears 2–3 months after gadolinium exposure. Other than renal failure, some reports emphasize the role of inflammatory states such as sepsis, osteomyelitis, endothelial damage (thrombosis or emboli), ischemia, and surgical complications on the development of NSF. Some studies have demonstrated a relationship between NSF and high doses of erythropoietin. Other studies have suggested that immunosuppression is a facilitating factor for NSF.

The low number of NSF patients among the large population with renal failure means that factors other than renal failure and gadolinium exposure could be involved in the development of NSF. The incidence of NSF is about 0.77% in renal failure patients when they are exposed to gadolinium. On average, 4.2% of dialysis patients who take gadolinium are at risk for NSF. Most patients with NSF have had severe chronic kidney disease (CKD) and have received hemodialysis. The clinical findings of NSF are similar to those in scleroderma. The lesions are progressive and painful with induration and often affect the lower limbs. The upper extremities and trunk are also involved; however, the face is spared. Involvement of the heart, lungs, liver, pleura, and joints has also been reported. The diagnosis of NSF is made by full-thickness skin biopsy. The 2-year mortality in dialysis patients with NSF is twice that of patients without the disorder (48% vs. 20%).

**MATERIALS AND METHODS**

The study was approved by the research board and ethics committee of Tehran University of Medical Sciences. All data from patients with serum creatinine levels >1.5 mg/dL who underwent magnetic resonance imaging/angiography (MRI/A) with gadolinium between 2006 and 2008, were extracted from the electronic database of the Tehran Heart Center. All patients were referred for different heart diseases. Among 6780 patients who were exposed to gadolinium, 344 met the criteria (>1.5 mg/dL). Unfortunately, only 164 patients were available or willing to be enrolled in the study.

At the time of the study, Magnevist (gadopentetate) (Schering A.G., Berlin-Wedding, Germany) was the only gadolinium chelate available. All patients received 0.1 mmol/kg contrast agent and none had repeated exposure to the agent. All patients were clinically reviewed by two physicians under the supervision of a nephrologist or dermatologist. The known symptoms and signs of NSF were looked for and recorded. If there was any doubt about the findings, patients were called back in and visited by a nephrologist. For the third time, a dermatologist was placed in charge of the patient if the lesions remained after symptomatic nonspecific therapy. The laboratory data were collected at the time of gadolinium exposure and during patient visits. The average time for visiting was 7 months after gadolinium exposure (range 4–18 months) and they were visited at 2- to 4-month intervals if they needed a second or third visit. Sixty-one patients were visited twice, seven three times, and one a fourth time.

All data were collected and analyzed using SPSS version 11.5. Parametric data were analyzed using paired two-tailed Student’s t-tests, and categorical data were analyzed using a χ²-test or Fisher’s exact test.

**RESULTS**

**Patient Characteristics**

One hundred and sixty-four patients were enrolled into the study (117 male and 47 female; 72% and 38%, respectively). The mean patient age was 68.53 ± 10.53 years old at the time of gadolinium exposure. The mean serum creatinine level was 2.14 ± 0.8 mg/dL, which gave a mean estimated glomerular filtration rate (eGFR) of 35.43 ± 16 mL/min, according to the Cockcroft–Gault formula. The criteria of Acute Kidney Injury Network were chosen for the definition of acute kidney injury (AKI). All patients were categorized into CKD stages 1–5 (Table 1).

**Skin Lesions**

No NSF lesions were found in our patients. Sixty-one patients (37%) had different skin problems. Table 2 shows the skin lesions and their severity in patients with different stages of CKD. Itching was the most common symptom and induration and woodiness of the skin and bullae were the least frequent. The lower limb was the predominant site of involvement (29 cases) followed by upper extremities (22 cases). Sixteen patients had trunk and abdominal skin lesions, but no patient had facial problems. Twelve patients had severe lesions, 24 had moderate, and 15 had mild. Upon clinical examination, there was a suspicion of lung and abdominal involvement, which was ruled out by sophisticated paraclinical and radiological evaluation.

None of the patients had typical NSF findings and all of those with some noncharacteristic skin lesions showed improvement with nonspecific or specific dermatological treatment. As a result of some reports regarding the relationship between liver diseases and NSF, liver function tests, prothrombin time, and serum albumin were measured in all patients. There was no relationship between these results and nonspecific skin lesions.

Only five patients were taking erythropoietin at the time of gadolinium exposure, and there was no relationship between the use of erythropoietin and its dose.
and skin findings. There was also no statistical significant association between eGFR and skin lesions. We did find a significant association between hemoglobin and CKD stage, but there was no relationship between hemoglobin and skin lesions.

GFR Changes
Generally, all eGFR categories were reduced during the study. However, the decline in eGFR was significant only in the CKD stage 4 group \( (p = 0.001) \). Three patients were on dialysis at the time of gadolinium exposure (two hemodialysis and one peritoneal dialysis); one of whom was diagnosed with AKI that improved after seven sessions of hemodialysis, but he/she still had moderate renal failure. We found that 42 patients (25%) had AKI. Five patients improved completely and now have normal renal function; however, although they had significant improvement of eGFR, 36 patients still had some degree of renal failure (CKD stages 2–3) at the end of the study. A total of nine patients progressed to ESRD and are now receiving dialysis.

Mortality
Thirty-one patients died during the study [21 (34%) with CKD stage 4, 5 (6%) with CKD stage 3, 4 (50%) with CKD stage 5, and 1 (8%) with CKD stage 2]. The rate of mortality in CKD stages 4 and 5 was significantly higher than in other groups \( (p < 0.0001 \) and \( p < 0.02 \), respectively). This incidental finding emphasized that simultaneous heart and kidney disease is associated with high mortality. None of the patients who died had NSF.

DISCUSSION
We did not find any NSF in our patients who were suffering from different stages of CKD. This emphasizes that factors other than renal failure and gadolinium could play a role in the development of NSF. It is not yet known why only a small number of patients with renal failure and gadolinium exposure develop NSF.

There is no specific test for the diagnosis of NSF, and examining blood or tissue samples for gadolinium is not possible in most centers worldwide. Therefore, a definite diagnosis of NSF is problematic and suspicion is aroused when the characteristic skin lesions become apparent. Thus, without performing a skin biopsy, the incidence of NSF in dialysis patients is probably lower than it is prevalent, and most of these patients are treated for diagnosis other than NSF. In a study in which only clinical findings, but not skin biopsy, were considered as the diagnosis criteria, it was shown that rather than 2.4% of dialysis patients, 13% of them were involved.\(^16\) Due to raising concerns about the NSF it seems that its incidence has markedly decreased. In this regard, Altun et al.\(^18\) have reported that the incidence of NSF in dialysis patients is probably lower than it is prevalent, and most of these patients are treated for diagnosis other than NSF. In a study in which only clinical findings, but not skin biopsy, were considered as the diagnosis criteria, it was shown that rather than 2.4% of dialysis patients, 13% of them were involved.\(^16\) Due to raising concerns about the NSF it seems that its incidence has markedly decreased. In this regard, Altun et al.\(^18\) have reported that the incidence of NSF has dropped from 3% to 0% in high-risk patients.

In the literature, most discussions focus on the incidence, histology, probable pathological mechanisms, and treatment strategies, and there are no sufficient data regarding the clinical course of NSF. We attempted to follow our patients over a long period according to the clinical findings and to show that nonspecific signs and symptoms like itching cannot be ignored; however, without other more specific findings such as induration and woody skin, these symptoms may be due to other diseases rather than NSF.

Another important issue in NSF is renal dysfunction. Renal failure together with gadolinium exposure is considered as a necessary element of NSF; nevertheless, it is not yet known which type and degree of renal failure are important for NSF development. Most patients with NSF are dialysis patients (80%), and the remaining 20% have had CKD stage 5 or AKI. However, there
are controversies about AKI as to whether it is a risk factor for NSF. Many studies have not reported NSF in patients with CKD stages 1–4 and few studies have reported NSF in patients with glomerular filtration rate (GFR) of 15–60 mL/min. In our study NSF was not seen in patients with mild-to-moderate renal failure or even in patients with a GFR >15 mL/min who had good urine volume. Generally, we can say that patients with CKD stage 2 or 3 have a low risk for NSF when they are exposed to gadolinium. According to our study, which examined a considerable number of patients with CKD stage 4, this degree of kidney disease does not increase the risk for NSF with gadolinium exposure. However, because some studies have reported NSF in these patients, we cannot definitely say that exposure to gadolinium does not pose any risk.

The type of gadolinium chelate is also important in the pathogenesis of NSF. Gadodiamide and gadopentetate dimeglumine are two common gadolinium chelates that are used. These two gadolinium chelates have the highest risk for NSF and most patients with NSF have taken gadodiamide or gadopentetate. NSF has also been reported with gadobenate, which is known to be an unstable chelate. The prevalence of NSF in patients with CKD stage 5 who underwent imaging with gadodiamide and gadopentetate was 18% and 30%, respectively. All of our patients had been taking gadopentetate.

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) have published advisory statements regarding gadolinium usage. According to the FDA, the use of OptiMARK, Omniscan, and Magnevist is contraindicated in patients with CKD with GFR <30 mL/min and in patients with AKI or during the peri-liver transplantation period. EMEA has announced that the use of high-risk gadolinium (Magnevist, Omniscan, OptiMARK, Magnevita, or Gado-MRT-ratiopharm) is contraindicated in severe renal failure patients, but moderate-risk gadolinium (Multi-Hance, Primovist, or Vasovist) and low-risk agent (ProHance, Gadovist, or Dotarem) can be used with warnings.

According to our study, Magnevist is safe in patients with GFR >30 mL/min and may be used with caution in patients with GFR 15–30 mL/min. Some investigators have banned gadodiamide in all patients with CKD stage 4 or 5 and they advise the use of non-gadodiamide contrast agents in these patients. Some believe that new macrocyclic gadolinium chelates with greater stability and contrast affinity as compared with older chelates are the preferred agents in such high-risk patients with GFR <25 mL/min. We have three choices in vascular evaluation of patients with CKD stage 4 or 5: (1) MRI without gadolinium, (2) computed tomography with iodinated contrast agents, and (3) the use of low-risk gadolinium agents. The first option has no benefit for the accurate diagnosis of vascular lesions. The second option is associated with known hazardous complications. Thus, the third possibility may be the option of choice in these high-risk patients.

Although 65 patients in our study had GFR <30 mL/min, the use of high-risk gadolinium did not cause NSF. It may be related to the dose of contrast agent and single use of gadopentetate. Nearly all reported patients with NSF had taken a greater dose of gadolinium than we used in our patients and some of the patients with NSF received gadolinium during several occasions. It may be that single use of such a low dose of high-risk gadolinium is safe in CKD stage 4 patients. The contrast quality of imaging is also good with this low dose of gadolinium. Currently, newer formulations of macrocyclic type agents such as gadoteridol and gadoterate dimeglumine with good stability are being administered in Europe. However, their safety should be evaluated in further studies. In contrast to some studies that have reported a high rate of NSF, no patients in our study with different CKD stages had NSF. Our study is comparable with those of Hope et al. and Janus et al., which also observed no NSF in patients with mild-to-moderate renal failure.

There are several limitations to our study: there were small numbers of ESRD patients. It will be impossible to study these patients in the future due to ethical issues. The other limitation was that the patients were diagnosed clinically rather than by skin biopsy. In a study by Mendoza et al., it has been shown that 30% of patients who were taking gadopentetate had skin lesions suggestive of NSF. Although they had not also biopsied these lesions, the patients had higher mortality than those without such lesions. They concluded that physicians likely underestimate the exact rate of NSF. We attempted to overcome this limitation by visiting the patients with two physicians under the supervision of a nephrologist or dermatologist, and any doubtful lesions were examined by an expert physician during repeated visits. Therefore, we can say that the probability of missing NSF in our study was near 0. In addition, there were several patients who met the enrollment criteria, but they did not come to us and we cannot say whether they had NSF. This was a retrospective study, but again, because of ethical issues, it is not possible to conduct further prospective studies of gadolinium treatment. Early death was observed in some patients with GFR <30 mL/min. Although they had no sign of NSF at the time of death, NSF may have been identified if they lived longer. The power of our study was the number of patients with AKI, which was a unique feature compared with other studies.

CONCLUSION

Although gadolinium is considered to be a causative agent of NSF in patients with renal failure, we suggest that single use of low-dose, high-risk gadolinium is safe in patients with CKD stages 1–3, and in those

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with CKD stage 4 with very low risk for NSF. It does not seem that AKI per se is a risk factor for NSF, particularly if kidney function is preserved thereafter. Because the NSF is a rare disease and other causes rather than renal failure and gadolinium may play a role in its development, more studies must be performed to explore the role of these conditions.

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REFERENCES


