Incidence of NSF at Two Large Medical Centers

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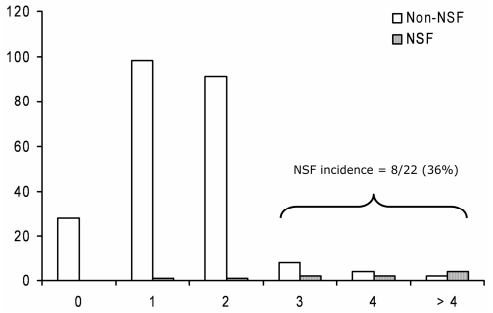
Introduction: Limited data on Nephrogenic Systemic Fibrosis (NSF) incidence and techniques for risk reduction, have hampered decision making in weighing risk versus benefit of GBCA enhanced MRI compared to alternative studies. To determine the incidence of NSF in patients undergoing GBCA enhanced MR and associated risk factors we retrospectively reviewed the past 10 years of patient records at two large hospitals.

Methods: MRI records from January 1, 1997 to June 30, 2007 were reviewed to determine the total number of patients undergoing GBCA enhanced MR exams at standard dose (0.1 mMol/kg) and high dose ($\geq$ 0.2 mMol/kg). Dermatopathology records were reviewed to identify biopsy-confirmed cases of NSF. For each NSF case, hospital records were reviewed to determine the time of symptom onset and the patient's clinical condition. Renal function status, arterial blood gas results as well as pro-inflammatory events near the time of MRI or symptom onset were also recorded. Since NSF cases were only found in patients following high dose GBCA injection, further analysis of hospital records was performed for these patients to determine their estimated glomerular filtration rate (eGFR) at the time of GBCA enhanced MR by utilizing the MDRD GFR equation.

Results: 25 biopsy-confirmed cases of NSF included 10 males and 15 females ranging in age from 13 to 82, of which 17 were on or just beginning hemodialysis. The remaining 8 patients not on dialysis had eGFR ranging from 6 ~ 27 mL/minute (mean = 15). Exposure to GBCA within 4 months prior to symptom onset was identified in 18 of 25 cases (72%) receiving high dose gadodiamide (30 ~ 60 mL), and mean time between gadodiamide injection and symptom onset was 54 (15-102) days. Five cases had no record of prior GBCA exposure and in two cases, remote exposure 19 months and 36 months prior to NSF was identified. In all 25 NSF patients, concomitant pro-inflammatory disease processes were present either at the time of gadodiamide injection or near the time of symptom onset including major surgery (n = 15), vascular surgery (n = 1), venous thrombosis (n = 3) and myocardial infarction (n = 2) and active SLE (n = 4). Three of the patients had antiphospholipid antibody syndrome.
GBCA enhanced MR studies were performed on a total of 83,150 patients. NSF incidence for various sub-populations is listed in Table 1. Gadodiamide (GE Healthcare, Princeton, NJ) was utilized on a total of 8025 exams at high dose, of which 833 had either eGFR < 30 mL/min (n = 576) or were on hemo- or peritoneal dialysis (n = 242 and 15 respectively). This group had 18 cases of NSF with an incidence of 0.22% for high dose gadodiamide overall and an incidence of 2.2% in those with both high dose gadodiamide and severe renal dysfunction [eGFR < 30 mL/min or on dialysis]. None of the 63,597 patients receiving standard dose gadodiamide acquired NSF.

A total of 81 patients had acute renal failure at the time of high dose GBCA administration; 9 received Gd:DTPA and 72 received gadodiamide. Seven patients with acute renal failure developed NSF after high dose gadodiamide injection. This corresponds to an incidence of 9.7% (7/72), which is significantly higher than the 1.4% (11/761) incidence of NSF in chronic renal failure receiving high dose gadodiamide ($p < 0.001$) and also significantly higher than the 1.2% incidence for patients with chronic severe renal failure but not yet on dialysis ($p < 0.001$). The mean interval between GBCA administration and the next dialysis treatment was 1.6 ± 1.3 days in patients who did not develop NSF compared to 4.6 ± 3.0 days in the patients who developed NSF ($p < 0.01$) (see Figure 1). There was only 1 case of NSF when dialysis was performed within 1 day after gadodiamide injection (1/127, 0.8%) but the risk was 8/22 (36%) when dialysis was delayed by 3 days or more ($p < 0.001$), see Figure 1. There were no cases of NSF when dialysis was performed the same day following high dose gadodiamide enhanced MRI. Reasons for delay in dialysis by 3 days or more included new initiation of dialysis after MR (n = 15), twice per week dialysis schedule (n = 5) and patient failure to show up for dialysis appointment (n = 2). Differences in risk between the contrast agents were not statistically significant.

Figure 1. Effect of the number of days between high dose gadodiamide injection and dialysis on NSF incidence. There were no cases of NSF for patients undergoing dialysis on the same day following higg-dose GBCA enhanced MR (column labeled zero). Greater delay between high-dose gadodiamide injection and dialysis increased the risk of NSF.



Conclusion: NSF risk in patients receiving standard dose GBCA without any screening for renal function is very small, 0 in 74,124 (0 in 63,597 for Gadodiamide). By screening to identify patients on dialysis or with severe renal insufficiency, eGFR < 30 mL/min, NSF can be virtually eliminated when these patients need GBCA enhanced MRI or MRA. First of all, avoid injecting GBCA into these patients during the period of any pro-inflammatory events. Second, use only standard dose, 0.1 mMol/kg. Finally, if the patient is on dialysis, arrange for dialysis to occur within 24 hours following MRI and preferably immediately following the MRI. When using standard dose gadodiamide, the risk of NSF is less than the risk of death from iodinated contrast injection for CT. Consequently, physicians should not automatically switch from GBCA enhanced MRI to iodinated contrast enhanced examinations to avoid NSF.

Table 1. NSF incidence	Incidence (number of exams, incidence)			
Patient population	Gadodiamide	Gd:DTPA	Gadobenate dimeglumine	Gadoteridol
Total	18/71622 - 0.025%	0/8683	0/2619	0/226
Standard dose	0/63597	0/7702	0/2619	0/206
High dose	18/8025 - 0.22%	0/981		0/20
eGFR < 30 mL/min	7/576 – 1.2%	0/117		0/9
eGFR < 15 mL/min	3/129 – 2.3%	0/19		
Hemodialysis	11/242 - 4.5%	0/36		0/4
Peritoneal dialysis	0/15	0/4		0
Delay to dialysis > 2 days	8/22 – 36.4%	0/6		

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