

PATIENT SAFETY

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The Risk of Acute Radiocontrast-Mediated Kidney Injury Following Endovascular Therapy for Acute Ischemic Stroke Is Low

BACKGROUND AND PURPOSE: Endovascular therapy is an alternative for the treatment of AIS resulting from large intracranial arterial occlusions that depends on the use of iodinated RCM. The risk of RCM-mediated AKI following endovascular therapy for AIS may be different from that following coronary interventions because patients may not have identical risk factors.

MATERIALS AND METHODS: All consecutive patients with large-vessel AIS undergoing endovascular therapy were prospectively recorded. We recorded the baseline kidney function, and RCM-AKI was assessed according to the AKIN criteria at 48 hours after RCM administration. We compared the rate of RCM-AKI 48 hours after the procedure and sought to determine whether any preexisting factors increased the risk of RCM-AKI.

RESULTS: We identified 99 patients meeting inclusion criteria. The average volume of contrast was 189 ± 71 mL, and the average creatinine change was -4.6% at 48 hours postangiography. There were 3 patients with RCM-AKI. Although all 3 patients died as a result of their strokes, return to baseline creatinine levels occurred before death. There was a trend toward higher rates of pre-morbid diabetes mellitus, chronic renal insufficiency, preadmission statin and NSAID use, and a higher serum creatinine level on admission for the RCM-AKI group. The volume of procedural contrast was similar between groups (those with and those without RCM-AKI) ($P = .5$).

CONCLUSIONS: In this small study, the rate of RCM-AKI following endovascular intervention for AIS was very low. A much larger study is required to determine its true incidence.

ABBREVIATIONS: ACS = acute coronary syndrome; AIS = acute ischemic stroke; AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; CAS = carotid angioplasty and stenting; IA = intra-arterial; IQR = interquartile range; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; mRS = modified Rankin Scale; NSAID = nonsteroidal anti-inflammatory drug; NSD = not sufficient data for P value computation; PROACT = Prolyse in Acute Cerebral Thromboembolism; RCM = radiocontrast media; tPA = tissue plasminogen activator

Endovascular techniques are available as therapeutic alternatives for the acute treatment of ischemic stroke. Intra-arterial thrombolysis and mechanical thrombectomy with the Merci retriever (Concentric Medical, Mountain View, Cali-

fornia)¹⁻⁴ or the suction catheter (Penumbra, Alameda, California)⁵ are aimed at reopening large proximal intracranial arterial occlusions due to thromboembolism. These techniques, however, depend on the use of iodinated RCM for microcatheter guidance and microguidewire manipulation. Through either tubular acidosis, ischemic injury from reactive oxygen species, and/or decreased medullary flow, RCM can lead to AKI.⁶⁻⁸ The third most common cause of AKI in hospitalized patients is RCM administration.⁹ Much of the data on RCM-AKI risk factors come from coronary angiography literature.¹⁰⁻¹² Because patients with cardiovascular disease are not identical to those at risk for acute ischemic stroke,¹³ we attempted to identify the risk factors for developing RCM-AKI following endovascular therapy for AIS.

Materials and Methods

All consecutive patients undergoing endovascular therapy for acute ischemic stroke were prospectively entered into the data base of our institution from September 2002 to January 2008, according to protocol approved by our local institutional review board. All patients or their proxies gave written informed consent.

Patients were included if they had a preintervention serum creatinine value and one 48 hours after intervention. We defined RCM-AKI according to the AKIN criteria,¹⁴ which is a relative increase of 50% or an absolute increase of 0.3 mg/dL ($28.2 \mu\text{mol/L}$) in the serum creatinine level at 48 hours following angiography compared with the

Received January 23, 2010; accepted after revision March 15.

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, the Department of Defense, or the United States government.

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indicates article with supplemental on-line table.

DOI 10.3174/ajnr.A2136

baseline admission level. Alternatively, oliguria of <5 mL/kg/h for >6 continuous hours can also be used as a diagnostic criterion. Patients with the diagnosis of AKI were included if the cause of the AKI was clearly a result of RCM administration. We dichotomized the study cohort into those with and without RCM-AKI.

The patient's age, sex, and time to endovascular therapy were compared between the groups. We also compared the distribution of the premorbid medical conditions of hypertension, diabetes mellitus, dyslipidemia, peripheral vascular disease, chronic renal insufficiency, prior stroke, and cardiac disease. We also compared rates of preadmission NSAID use and admission glucose levels.

We then compared select elements of the endovascular intervention, specifically the elapsed time from symptom onset to endovascular therapy and the total volume of contrast (Omnipaque [iohexol], 300 mgI/mL; GE Healthcare, Princeton, New Jersey). If patients underwent CT angiography or perfusion, the volume of contrast (also Omnipaque 300) was added to the cumulative dose. We compared the rate of successful total or partial recanalization as well as the rate of hemorrhagic transformation in the 72-hour period following intervention.

Statistical analyses for categorical variables included the Fisher exact test. Median values with an IQR were calculated for unevenly distributed categorical variables and compared by using the Mann-Whitney *U* test. All analytic procedures were conducted in R, Version 2.10.0 (<http://www.r-project.org/>).

Results

We identified a total of 100 patients with AIS treated with endovascular therapy. One patient was excluded because her course was complicated by immediate postprocedural retroperitoneal hemorrhage resulting in hemorrhagic shock, and the subsequent azotemia and oliguria were deemed a result of this condition. Ninety-nine patients, therefore, made up in this cohort including those treated with the Merci retriever ($n = 91$; 6 with adjuvant IA tPA, 1 with adjuvant CAS, 3 with adjuvant intracranial balloon angioplasty), CAS only ($n = 2$), primary intracranial balloon angioplasty ($n = 3$; 2 with adjuvant IA tPA), intra-aortic NeuroFlo balloon catheter inflation ($n = 1$; CoAxia, Maple Grove, Minnesota), and IA tPA only ($n = 2$). All patients received intravenous hydration with normal saline.

The mean age was 64.9 ± 19.3 years of age, and 47 were men. The mean preangiography serum creatinine level was 0.9 ± 0.3 mg/dL, the average volume of contrast was 189 ± 71 mL, and the 48-hour postangiography creatinine level was 0.9 ± 0.3 mg/dL ($P = .4$ compared with admission creatinine). The average creatinine change was -4.6% at 48 hours postangiography.

There were 3 cases of AKI. Two of these patients met AKIN diagnostic criteria by absolute but not relative serum creatinine increase, while the other met both creatinine change criteria. The absolute (and relative) changes in creatinine levels were as follows: 0.4 mg/dL ($+33.3\%$), 0.3 mg/dL ($+27.3\%$), and 1.0 mg/dL ($+76.9\%$). The first patient met oliguria criteria within the initial 48-hour assessment period for >24 hours (stage III). On average, patients with RCM-AKI had a creatinine increase of 0.7 mg/dL ($+62\%$) 48 hours after angiography.

All the patients in the RCM-AKI group were male (100% versus 44%, $P = .1$), but the mean age of each subgroup was

similar (On-line Table). In the RCM-AKI group, there was a trend toward higher rates of premorbid history of diabetes mellitus (66% versus 17%, $P = .08$) and chronic renal insufficiency (33% versus 2%, $P = .1$). There was a higher incidence of preadmission use of statins (66% versus 20%, $P = .1$) and NSAIDs (66% versus 30%, $P = .1$) in the RCM-AKI group. The RCM-AKI group showed higher admission serum creatinine levels (1.2 ± 0.1 versus 0.9 ± 0.3 , $P = .02$), while admission serum glucose levels were similar (147 ± 17 versus 140 ± 61 , $P = .5$). The volume of contrast administered intraprocedurally was similar between groups (185 ± 59 mL versus 313 ± 241 mL, $P = .5$). There was no difference in the rate of successful recanalization or hemorrhagic transformation at 72 hours.

Of the 3 patients with RCM-AKI, none developed anuria, but 1 became oliguric. The 2 nonoliguric patients with RCM-AKI were managed conservatively with IV hydration, while the oliguric patient required continuous furosemide infusion with eventual return of kidney function and normalization of his azotemia. No patient required hemodialysis. Although all 3 patients died as a result of their strokes, their creatinine levels all returned to their baseline levels before death.

Discussion

In this small study, the risk of RCM-AKI in the patient with AIS undergoing endovascular therapy was very low (3%) with minimal significant long-term clinical consequences. Although the incidence reported in the literature concerning endovascular interventions for ACS ranges from 10% to 20%,¹⁵⁻¹⁷ our small study size makes it impossible to make a fair intercohort comparison. A much larger study is required to determine the true incidence of RCM-AKI in endovascularly treated patients with AIS before such comparison can be made.

In the coronary angiography population, known associations with RCM-AKI include the use of ionic RCM, higher baseline serum creatinine levels, male sex, a history of diabetes mellitus, volume of contrast agent, and chronic renal insufficiency.^{18,19} In other studies of patients receiving RCM during coronary angiography, associations with RCM-AKI include increased age, preprocedural hypovolemia, congestive heart failure, cirrhosis, proteinuria, IA RCM administration, prior NSAID use, and hypertension.¹²

The development of RCM-AKI is associated with prolonged hospitalization, adverse cardiac events, and increased mortality. However, this may be an epiphenomenon of the severity of underlying cardiac and comorbid systemic conditions. Patients with RCM-AKI who require hemodialysis have a high in-hospital mortality.¹²

The data from this cohort are descriptive in nature but can serve as a useful means to compare RCM-AKI in patients with AIS and ACS undergoing intervention. The RCM-AKI incidence observed in the present study compares favorably with the 10%–20% in the ACS population. The RCM-AKI incidences in the 3 most recent coronary intervention studies are all higher than that observed in our cohort: 11.5% (45/392, $P = .008$) reported by Wickenbrock et al,¹⁵ 10.2% (41/400, $P < .03$) reported by Jabara et al,¹⁶ and 20.5% (115/561, $P < .0001$) reported by Marenzi et al.¹⁷ In pooling the 201 separate

instances identified in the total of 1353 coronary interventions, the finding of the present study of 3 cases in 99 instances is markedly lower ($P < .001$).

One key difference in the populations undergoing intervention for ACS versus AIS, however, may be the higher distribution of atherosclerosis and underlying chronic renal insufficiency in the former group. The overall incidence of renal insufficiency on admission (defined as baseline serum creatinine level, ≥ 1.5 mg/dL) was 5% (5/99) in our cohort, which compares favorably with the 30.5% rate (171/561, $P < .0001$) in the report by Marenzi et al.¹⁷

Differences in the distribution of renal insufficiency alone may not account for the higher rate of RCM-AKI in patients with ACS undergoing intervention. In a subset of patients with normal baseline creatinine levels, $>8\%$ of patients undergoing coronary intervention experienced RCM-AKI.^{18,20}

Renal insufficiency on admission, however, is likely due to a different etiology in patients with AIS compared with those with ACS. Patients with AIS may present more frequently in a prerenal hemoconcentrated state with acute glomerular insufficiency.²¹ In patients with such prerenal azotemia, glomerular filtration can be normalized with hydration, unlike patients with azotemia from intrinsic renal disease such as those with ACS. None of the 5 patients in our cohort with elevated pre-intervention creatinine levels developed RCM-AKI, while in fact, all had decreased serum creatinine levels at 48 hours. Furthermore, half (50/99) of all patients in our cohort similarly had a decrease in the serum creatinine level at 48 hours, indicating that patients with AIS may present with dehydration or even that dehydration may predispose certain patients to AIS. Forty-eight-hour reductions in serum creatinine levels may be due to the aggressive rehydration that all patients with AIS receive. In addition, our center is a tertiary stroke care facility, and most of the patients treated endovascularly were transferred from outside institutions. Because the average time to intervention was >6 hours, this may imply a period of de facto preprocedural hydration in those patients undergoing transfer.

One of several other differences between patients with ACS and AIS is the higher incidence of cardiogenic shock in the former group. This complication was a rare observation in our cohort but occurred in 12% of the ACS population studied by Marenzi et al.¹⁷ Second, distal aortic embolization and subsequent renal arteriolar occlusion are a risk of intervention for ACS and less so for AIS. Cholesterol embolization can cause AKI immediately following coronary intervention and is difficult to distinguish from true cases of RCM-AKI.¹² Inclusion of such cases would overestimate the true rate of RCM-AKI following coronary intervention. Finally, the procedural contrast requirement for coronary intervention may be routinely higher than that for endovascular AIS therapy. In fact, this held true because the contrast in the study by Marenzi et al.¹⁷ was 265 ± 130 mL, significantly higher than the 189 ± 71 mL administered in our cohort ($P < .0001$).

In our cohort, any relationship between RCM-AKI and renoprotective-agent administration was indeterminate. Although statin use has been documented to be renoprotective against RCM-AKI,²² we demonstrated a trend toward a higher incidence of statin use in the RCM-AKI group (66% [2/3] versus 20% [19/95], $P = .1$). Although the evidence for N-

acetylcysteine as a renoprotective agent is debated,²³⁻²⁵ it was neither a variable prospectively tracked in our data base nor is it routinely used before emergent intervention at our institution.

Our study was notably limited by the fact that only 3 patients had RCM-AKI, only 1 of whom was oliguric. Thus, no meaningful analysis could be made in regard to independent risk factors through multivariate analysis. In the RCM-AKI subset, we noted a trend towards diabetes and chronic renal insufficiency, consistent with prior reports. However, for meaningful numbers able to power a multivariate analysis, calculating from the strongest association, diabetes, and assuming a 50% incidence of diabetes within the RCM-AKI subset, one would need a total of 18 patients with RCM-AKI. At a 3% incidence rate, this would require 500 more patients with AIS to undergo endovascular therapy, nearly the pooled sample size of the entire multicenter PROACT, PROACT II, MERCI, and Multi MERCI cohorts.^{1,2,4,26} Pooling these previous endovascular studies for analysis may be worthwhile in an endeavor to compare independent risk factors by using multivariate analysis.

Another variable beyond our control was the extent of intravenous hydration before angiography. RCM-AKI prevention is widely debated, and particularly in emergent situations such as AIS, little evidence exists to support any beneficial preventative therapies or techniques other than adequate rehydration and the judicious use of low-osmolality contrast agents.²⁵ Despite the fact that all patients had a period of intravenous rehydration before catheterization, there was no way to assess the rate or total volume of fluid resuscitation.

Our small study size and low overall RCM-AKI rate combined make meaningful comparisons difficult. As an example, the 3 patients with RCM-AKI have a wide range of administered contrast volume (313 ± 241 mL), and this wide deviation precludes detection of any statistical difference from the mean of 185 mL in the patients who did not have RCM-AKI, though the mean is nearly 1.5 times greater. We are not suggesting that our data imply that a larger study would necessarily demonstrate a similar lack of difference, but we are suggesting that one is needed to confirm that the RCM-AKI incidence following endovascular therapy for AIS is truly as low as that demonstrated in our cohort.

Our observational data can also only be descriptive of the true incidence of hemodialysis-requiring RCM-AKI in endovascularly treated patients with AIS. No patient with RCM-AKI in our cohort required hemodialysis, compared with 12/561 (2%) of the patients studied by Marenzi et al.¹⁷ Because such severe RCM-AKI is associated with higher rates of in-hospital mortality,¹² the absence of this requirement in our study population suggests that the true incidence may in fact also be very low, a relevant fact when assessing the overall risk to the patient.

Despite the inability to establish a relationship between RCM-AKI and functional outcome in this study, it is still noteworthy to analyze overall outcome data to compare risk and benefit. In this small sample, 34% (33/97) had a good or excellent outcome ($mRS \leq 2$). Given the 3% risk of RCM-AKI, 30 eligible patients with AIS would need to be treated endovascularly to achieve 10 good outcomes at the risk of 1 case of

RCM-AKI. At this point in the early stages of endovascular therapy as a therapeutic option for AIS, we must rely on such descriptive observational data alone to make decisions regarding the overall benefit-to-risk ratio.

Conclusions

In this small study, the rate of RCM-AKI following endovascular intervention for AIS was very low. Because of both this low rate and the low overall occurrence of endovascular interventions for AIS, no concrete conclusions could be drawn regarding predisposing factors. There may be an increased risk with pre-morbid diabetes mellitus, chronic renal insufficiency, preadmission statin and NSAID use, and a higher serum creatinine level on admission. There are inherent differences in patients undergoing endovascular intervention for AIS and ACS that may explain why RCM-AKI rates in our study were lower than those for patients with ACS, but our small sample size precludes fair comparison. A larger study is required to determine the true incidence of RCM-AKI in the AIS population.

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