Prevention, Incidence, and Outcomes of Contrast-Induced Acute Kidney Injury

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Background: Little is known about whether health care providers (physicians) implement preventive care for contrast-induced acute kidney injury (CIAKI). The objectives of our prospective cohort study were (1) to assess provider use of preventive strategies for CIAKI, (2) to determine the incidence of CIAKI, and (3) to examine the association of CIAKI with adverse outcomes at 30 days, including death, need for dialysis, and hospital admission.

Methods: We prospectively identified patients with estimated glomerular filtration rates less than 60 mL/min/1.73 m² undergoing procedures with intravascular radiocontrast agents and recorded the use of intravenous fluids and N-acetylcysteine and the discontinuation of nonsteroidal anti-inflammatory medications. We measured postprocedure serum creatinine levels to quantify the incidence of CIAKI and tracked 30-day mortality and need for dialysis or hospitalization to evaluate the association of CIAKI with these outcomes.

Results: Preprocedure and postprocedure intravenous fluids were administered to 264 of 660 study patients (40.0%), more commonly with coronary angiography than with computed tomography (91.2% vs 16.6%, P < .001). N-acetylcysteine was administered to 39.2% of patients, while only 6.8% of patients using nonsteroidal anti-inflammatory drugs were instructed to discontinue the medication. In a propensity analysis, the use of intravenous fluids was associated with a reduced rate of CIAKI. The incidence of CIAKI was lowest following computed tomography (range, 0.0%-10.9%) and was highest following noncoronary angiography (range, 1.9%-34.0%). Eleven patients (1.7%) died, 1 patient (0.2%) required dialysis, and 83 patients (12.6%) were hospitalized; however, CIAKI was not independently associated with hospital admission or death.

Conclusions: Strategies to prevent CIAKI are implemented nonuniformly. Although biochemical evidence of CIAKI is relatively common, clinically significant CIAKI is rare. These findings should help health care providers focus on the use of preventive care on the highest-risk patients and have important implications for future clinical trials.

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were (1) to assess provider use of preventive strategies for CIAKI, (2) to determine the incidence of CIAKI, and (3) to examine the association of CIAKI with adverse outcomes at 30 days, including death, need for dialysis, and hospital admission.

**METHODS**

**PATIENT POPULATION**

We conducted a prospective observational cohort study of patients undergoing procedures involving the administration of intravascular iodinated radiocontrast agents at the Veterans Affairs (VA) Pittsburgh Healthcare System between February 1, 2005, and July 31, 2006. We identified all subjects scheduled to undergo CT with IV radiocontrast, coronary angiography, or noncoronary angiography in the inpatient or outpatient setting before the procedure. We recorded the serum creatinine (SCR) level measured most proximate to and within 60 days of the procedure and calculated patients’ baseline estimated glomerular filtration rate (eGFR) using the 4-variable Modification of Diet in Renal Disease study equation.14 Patients at the VA Pittsburgh Healthcare System are recommended to have SCR measurement at 48 to 96 hours after the procedure, informed consent was obtained.

For acute kidney injury was a radiocontrast agent, we excluded patients undergoing procedures involving the administration of radiocontrast media administered, immediate complications assessed using analysis of variance, Fisher exact test, and Kruskal-Wallis test as appropriate. To describe the use of preventive care, we report the proportion of patients who received preprocedure or/and postprocedure IV fluids and the proportion of patients who received isotonic fluid. We also report the proportion of patients administered N-acetylcysteine, the proportion of patients prescribed NSAIDs, and, among subjects who reported taking prescribed or over-the-counter NSAIDs, the proportion in whom these medications were discontinued.

We assessed the incidence of CIAKI using 3 non–mutually exclusive relative increments in the SCR level from baseline (≥25%, ≥50%, and ≥100%) and 3 non–mutually exclusive absolute changes in SCR levels from baseline (≥0.25, ≥0.5, and ≥1.0 mg/dL) (to convert SCR levels to micromoles per liter, multiply by 88.4). Among hospitalized patients with multiple postprocedure SCR measurements, the development of CIAKI was based on the maximal increase in SCR level within 96 hours. Although our study was not designed or powered to examine the protective effect of preventive care, we explored univariate associations of IV fluid administration, N-acetylcysteine use, and discontinuation of NSAIDs with the development of CIAKI using Fisher exact test. To account for clinical differences between patients who did and did not receive preventive strategies, we generated propensity scores using logistic regression models that predicted the use of each preventive measure. Patients were stratified by quintiles of the propensity score, and only those quintiles with adequate overlap between treated and non-treated patients were used in the analyses. Multivariate logistic regression analysis was used to assess the associations of the 3 preventive interventions with the development of CIAKI, adjusting for propensity score. For these analyses, we used 2 definitions of CIAKI as the dependent variable, an increase in SCR level of at least 0.5 mg/dL and an increase of at least 25%, as these have been the most commonly used definitions in prior studies. Unadjusted associations of CIAKI with mortality, need for dialysis, and hospitalization were assessed using Fisher exact test for each of the 6 definitions. Because of the low incidence of death, we used exact logistic regression analysis to examine the associations of CIAKI with mortality, adjusting for confounders that were found to have a univariate association (P ≤ .10) with this outcome. Two-sided P < .05 was considered to represent statistical significance. All analyses were conducted using commercially available statistical software (STATA version 9; StataCorp LP, College Station, Texas). The institutional re-
view board at the VA Pittsburgh Healthcare System approved all study procedures.

RESULTS

PATIENT AND PROCEDURE CHARACTERISTICS

We screened 11,410 patients undergoing radiographic procedures, of whom 1884 (16.5%) were scheduled to receive an intravascular radiocontrast agent and had a baseline eGFR less than 60 mL/min/1.73 m². Of these, 324 met exclusion criteria (17.2%), and 900 did not receive an intravascular radiocontrast agent, declined to participate, or were unavailable for recruitment, resulting in a study population of 660 patients (Figure 1). All 660 patients had baseline SCr levels measured within 60 days of the procedure, 440 had this test within 3 days before the procedure (66.7%), and 477 had this test within 7 days before the procedure (72.3%). Four hundred twenty-one patients (63.8%) underwent CT, 181 patients (27.4%) underwent coronary angiography, and 58 patients (8.8%) underwent noncoronary angiography. The mean age was 69 years, the median baseline eGFR was 52 mL/min/1.73 m², and 95.5% were men. Iso-osmolar radiocontrast (Iodixanol; GE Healthcare, Princeton, New Jersey), which is the primary agent used in patients with reduced eGFR at the VA Pittsburgh Healthcare System, was administered to 568 patients, and a low-osmolar radiocontrast agent (Iohexol, GE Healthcare) was administered to 92 patients (Table 1).

USE OF PREVENTIVE CARE

Overall, 282 patients (42.7%) received preprocedure IV fluids, 317 (48.0%) received postprocedure IV fluids, and 264 (40.0%) received both (more commonly with coronary angiography than with CT [91.2% vs 16.6%; P < .001]) (Figure 2). Isotonic fluid was administered to 83.7% of patients who received preprocedure fluids and to 62.5% of patients who received postprocedure fluids. Hospitalized patients and those undergoing coronary angiography were most likely to receive IV fluids (Table 2). One hundred thirty-two patients (20.0%) reported being told to increase their preprocedure oral fluid intake, and 103 patients (78.0%) described complying with this recommendation.

N-acetylcysteine was administered to 259 patients (39.2%), most commonly those undergoing coronary angiography; however, there was no standard protocol in place for the administration of N-acetylcysteine. Overall, 67 patients (10.2%) were prescribed NSAIDs, 44 patients (6.7%) reported taking these medications, yet only 3 (6.8%) of those who reported taking NSAIDs were instructed to discontinue the medication, all of whom were undergoing coronary angiography.

INCIDENCE OF CIAKI

Postprocedure SCr level was measured in 585 patients (88.6%), of whom 546 patients (93.3%) completed this test within 96 hours, while 39 patients (6.7%) had their SCr level measured on postprocedure day 5. These 39 patients were included in our assessment of CIAKI, as sensitivity analyses that excluded these subjects did not alter the study results. The incidence of CIAKI ranged from 0.2% to 7.7% based on relative increases in SCr levels of at least 100% to at least 25%, respectively, and from 0.7% to 13.3% with absolute changes in SCr levels of at least 1.0 mg/dL to at least 0.25 mg/dL, respectively (Table 3). Although the incidence of CIAKI was highest following noncoronary angiography and was lowest with CT, adjustment for baseline eGFR rendered these differences nonstatistically significant (data not shown).

30-DAY OUTCOMES

We collected 30-day outcome data by electronic medical record review for all 660 patients and were able to contact 427 patients (64.7%) for follow-up telephone interview. Eleven patients (1.7%) had died, 10 of whom had undergone CT and 1 of whom had undergone coronary angiography. Three of these 11 patients (27.39%) had developed CIAKI based on an increase in SCr level.
of at least 25% or at least 0.5 mg/dL. Only 1 patient (0.2%) required dialysis, and 83 patients (12.6%) were hospitalized within 30 days but not immediately following the index procedure. Only 1 hospital admission was related to renal failure but occurred in a patient who had not developed CIAKI.
ASSOCIATIONS OF PREVENTIVE CARE, CIAKI, AND 30-DAY OUTCOMES

In univariate analyses, the use of preprocedure and postprocedure IV fluid was not associated with a lower incidence of CIAKI. Analyses that adjusted for propensity scores estimated a protective effect of IV fluid, although this effect was statistically significant for only 1 definition of CIAKI, an increase in SCr level of at least 0.5 mg/dL (Table 4). Patients who received N-acetylcysteine were more likely to develop CIAKI than those who did not receive this agent, although propensity score adjustment rendered these differences nonstatistically significant. Discontinuation of NSAIDs was not associated with a lower rate of CIAKI, yet the few patients in whom these medications were discontinued significantly limited this analysis.

Table 2. Use of Preventive Care by Type of Radiographic Procedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N=660)</th>
<th>Computed Tomography (n=421)</th>
<th>Coronary Angiography (n=181)</th>
<th>Noncoronary Angiography (n=58)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprocedure intravenous fluids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall use, %b</td>
<td>43</td>
<td>20</td>
<td>92</td>
<td>55</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Isotonic sodium chloride</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>14</td>
<td>.60</td>
</tr>
<tr>
<td>Isotonic sodium bicarbonate</td>
<td>23</td>
<td>5</td>
<td>64</td>
<td>24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypotonic sodium chloride</td>
<td>7</td>
<td>2</td>
<td>13</td>
<td>17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Volume, median (interquartile range), mL</td>
<td>368 (250-900)</td>
<td>900 (300-1200)</td>
<td>258 (213-450)</td>
<td>740 (300-960)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postprocedure intravenous fluids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall use, %b</td>
<td>48</td>
<td>22</td>
<td>98</td>
<td>85</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Isotonic sodium chloride</td>
<td>13</td>
<td>14</td>
<td>9</td>
<td>15</td>
<td>.21</td>
</tr>
<tr>
<td>Isotonic sodium bicarbonate</td>
<td>17</td>
<td>4</td>
<td>41</td>
<td>43</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypotonic sodium chloride</td>
<td>18</td>
<td>4</td>
<td>48</td>
<td>27</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Volume, median (interquartile range), mL</td>
<td>450 (450-900)</td>
<td>900 (500-1200)</td>
<td>450 (450-450)</td>
<td>900 (600-1200)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>N-acetylcysteine use, %</td>
<td>39</td>
<td>17</td>
<td>84</td>
<td>59</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Discontinued nonsteroidal anti-inflammatory drugs, %c</td>
<td>7</td>
<td>0</td>
<td>21</td>
<td>. . . . . . . . 0 3</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ellipsis, not applicable.

* Simultaneously tests for differences between any of the 3 procedures.

b Sum of patients receiving each form of intravenous fluid may not equal overall use as patients may have received more than 1 type of intravenous fluid.

c Proportion of patients who reported taking nonsteroidal anti-inflammatory drugs in whom medication was discontinued.

Table 3. Incidence of Contrast-Induced Acute Kidney Injury (CIAKI) by Type of Radiographic Procedure

<table>
<thead>
<tr>
<th>CIAKI Definition Based on Change in Serum Creatinine Level</th>
<th>Overall (n=585)</th>
<th>Computed Tomography (n=367)</th>
<th>Coronary Angiography (n=165)</th>
<th>Noncoronary Angiography (n=53)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>7.7</td>
<td>6.5</td>
<td>8.5</td>
<td>13.2</td>
<td>.19</td>
</tr>
<tr>
<td>≥50</td>
<td>1.2</td>
<td>0.5</td>
<td>1.2</td>
<td>5.7</td>
<td>.02</td>
</tr>
<tr>
<td>≥100</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
<td>1.9</td>
<td>.09</td>
</tr>
<tr>
<td>mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.25</td>
<td>13.3</td>
<td>10.9</td>
<td>12.1</td>
<td>34.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥0.5</td>
<td>5.3</td>
<td>3.5</td>
<td>6.1</td>
<td>15.1</td>
<td>.004</td>
</tr>
<tr>
<td>≥1.0</td>
<td>0.7</td>
<td>0.3</td>
<td>0.6</td>
<td>3.8</td>
<td>.04</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert serum creatinine levels to micromoles per liter, multiply by 88.4.

a Simultaneously tests for differences between any of the 3 procedures.

Table 4. Associations of Preventive Care With Contrast-Induced Acute Kidney Injury (CIAKI)

<table>
<thead>
<tr>
<th>CIAKI Definition Based on Change in Serum Creatinine Level</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravenous Fluids</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusteda</td>
</tr>
<tr>
<td>≥25%</td>
<td>1.4 (0.8-2.6)</td>
<td>0.7 (0.3-1.5)</td>
</tr>
<tr>
<td>≥0.5 mg/dL</td>
<td>1.2 (0.6-2.5)</td>
<td>0.4 (0.2-1.0)</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert serum creatinine levels to micromoles per liter, multiply by 88.4.

a Adjusted for propensity score.
Contrast-induced acute kidney injury defined by a rise in SCr level of at least 0.5 mg/dL was associated with an increased risk for mortality in univariate analyses, although adjustment for cerebrovascular disease and status at the time of the procedure (hospitalized vs outpatient), which were each associated with an increased risk for death, rendered this association nonstatistically significant. The wide confidence intervals of these odds ratios reflected the small number of deaths (Table 5). In sensitivity analyses using a composite definition of CIAKI based on an increase in SCr level of at least 25% or at least 0.5 mg/dL, which has been a commonly used definition in past trials, CIAKI had no statistically significant association with mortality in univariate or adjusted analyses (data not shown). There was a marginally statistically significant univariate association of CIAKI defined by a rise in SCr level of at least 0.5 mg/dL with need for dialysis (P = .05), although these analyses were limited by so few patients who required renal replacement therapy. CIAKI was not associated with hospital readmission in univariate or covariate adjusted analyses (data not shown).

In this observational study of patients at increased risk for CIAKI undergoing contrast-enhanced radiographic procedures, preventive measures were implemented non-uniformly, with substantially greater use in hospitalized patients and in those undergoing coronary angiography. Although CIAKI occurred in a reasonable proportion of patients, adverse 30-day outcomes were uncommon. These findings should help direct the use of evidence-based preventive strategies to the highest-risk patients and have important implications for the design of future trials of CIAKI.

Intravascular volume expansion with isotonic fluid is arguably the most effective preventive intervention for CIAKI.11,12,15 We observed wide variation in the use and composition of IV fluid. More than 50% of patients failed to receive any IV fluid, while hypotonic fluid use constituted 37.5% of postprocedure fluid administration overall. Health care providers may use hypotonic fluids in some patients for fear of precipitating heart failure with the administration of fluid containing higher concentrations of sodium. However, this is likely to be clinically appropriate in few patients. Efforts to increase the administration of IV isotonic fluids in the highest-risk patients will help further decrease the incidence of CIAKI.

We also found nonuniform administration of N-acetylcysteine and almost universal lack of discontinuation of NSAIDs. Given the considerable debate on the benefit of N-acetylcysteine therapy, the variable implementation of this treatment in the present study may reflect uncertainty in the medical community regarding the benefit of this agent.8,9,16 However, discontinuation of NSAIDs was infrequently performed, despite expert recommendations to stop these medications before administration of a radiocontrast agent.11,12 Given the frequency at which NSAIDs are consumed by the general population, routine discontinuation of these agents is a simple and safe strategy to reduce patients’ risk for CIAKI.

Despite being less likely to receive preventive care, patients who underwent CT developed CIAKI less frequently than those who underwent angiography, particularly noncoronary procedures. This may be related to a higher baseline eGFR in these patients than in subjects who underwent noncoronary angiography. In fact, 254 patients who met initial inclusion criteria and were scheduled for CT with an IV radiocontrast agent underwent the procedure without vascular enhancement. This is likely reflective of decisions by radiologists to perform CT without an IV radiocontrast agent in higher-risk patients. Whether IV administration of a radiocontrast agent is less nephrotoxic than intra-arterial administration is an important clinical issue, as the provision of prophylactic IV fluid is considerably more challenging in subjects undergoing outpatient CT than in hospitalized patients or in those undergoing angiography. However, of 212 study patients who underwent outpatient CT and had a baseline eGFR of at least 45 mL/min/1.73 m², 5 patients (2.4%) experienced an increase in SCr level of at least 25%, 2 patients (0.9%) manifested a rise of at least 0.5 mg/dL, and none died. These findings suggest that the risk for clinically consequential CIAKI in patients with mild chronic kidney disease who are undergoing outpatient CT is low, even in the absence of preventive care. Given the practical and fiscal obstacles to routinely providing IV fluids to the majority of patients scheduled to undergo outpatient CT who are judged to be at risk for CIAKI, preventive protocols in the radiology setting should focus on those at highest risk. Moreover, future analyses should weigh the short-term benefits of avoiding an IV radiocontrast agent with the longer-term risks of underdiagnosis from lack of vascular enhancement.

We defined our patients as being at high risk for CIAKI based on a reduced baseline eGFR, yet few patients manifested robust elevations in SCr levels. Expert consensus panels have recommended, and many clinical trials have used, a baseline eGFR less than 60 mL/min/1.73 m² (or
creatinine clearance <60 mL/min) to categorize patients as high risk.6,12-17-21 Our findings indicate that patients with only mildly reduced eGFR are at low risk for CIAKI. The use of an eGFR less than 60 mL/min/1.73 m² as the threshold below which risk for CIAKI increases is consistent with the National Kidney Foundation’s definition of chronic kidney disease.22 However, in many older patients, reduced eGFR calculated using the 4-variable Modification of Diet in Renal Disease study equation may be a function of increased age than elevation in Scr level.14 Using an eGFR level less than 60 mL/min/1.73 m² to define increased risk may misclassify many patients with regard to true susceptibility for CIAKI.

Clinical trials have used small increments in Scr level to define CIAKI under the assumption that these changes are predictive of adverse outcomes.6,7,23-26 However, we found that adverse outcomes with CIAKI were uncommon. Although using small changes in Scr level as the primary end point in clinical trials allows for the enrollment of fewer patients and may inflate study “event rates,” it has likely contributed to the proliferation of small trials of sodium bicarbonate and N-acetylcysteine with inadequate numbers of clinically meaningful events that have confused rather than informed clinical decision making.23,24,20,26 We conducted post-hoc analyses to estimate the sample size necessary to accurately evaluate the efficacy of a hypothetical intervention in reducing mortality from 1.7%, which was the rate observed in our study, to 0.85%. Considering an α level of .05 and 90% power, more than 3700 patients would be required in each study arm. For future trials, investigators should define patients as high risk based on more advanced baseline renal insufficiency and should consider including the need for dialysis, hospital length of stay, and death in sample size estimations to derive clinically meaningful data on the efficacy of preventive interventions.

There are certain limitations to this study. First, our findings are based on a small sample size and clinical events from a single site, which limits generalizability to the full spectrum of patients at risk for CIAKI. Second, in addition to enrolling many patients with only mildly reduced eGFR, we excluded subjects with hypotension and patients undergoing emergent procedures, rendering most of our study population at lower rather than higher risk for CIAKI. Third, variability in the timing of postprocedure Scr assessments and the inclusion of patients with postprocedure Scr measurements at 96 hours and longer could have affected the accuracy with which we identified cases of CIAKI. Fourth, there may have been a Hawthorne effect with respect to the use of preventive care. However, if present, this would suggest that preventive strategies are used even less uniformly elsewhere. Fifth, we were unable to contact a substantial number of patients by telephone for 30-day follow-up and cannot be certain that we captured all 30-day outcomes. However, the use of the VA integrated electronic health record, which records care delivered at all VA facilities, likely enabled us to identify most postprocedure events. Patients with lower baseline eGFR were more likely to receive IV fluids and N-acetylcysteine, suggesting that operator bias, in which health care providers are more likely to implement preventive care in higher-risk patients, may have masked the true beneficial effect of such care.

In conclusion, this study demonstrates nonuniform implementation of preventive care for CIAKI. Patients undergoing CT were least likely to receive preventive interventions but demonstrated the lowest rate of CIAKI. These findings will help health care providers determine which patients are the most likely to derive benefit from preventive measures. The low incidence of clinically consequential CIAKI is a novel observation that will help physicians and patients make informed decisions on the risks and benefits of radiocontrast administration and should assist investigators in designing adequately powered clinical trials to advance our understanding of how to most effectively prevent this iatrogenic condition in patients at greatest risk.

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