Contrast-Induced Nephropathy in Ischemic Stroke Patients Undergoing Computed Tomography Angiography: CINISter Study

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Goal: Computed tomography angiography (CTA) is a well-tolerated, noninvasive study of the intracranial vascular circulation; however, contrast-induced nephropathy (CIN) has been reported in 5%-7% of patients undergoing CTA. Limited studies have evaluated the risks of CIN in patients undergoing CTA. Our study was designed to evaluate the prevalence and risk factors for CIN in patients with ischemic stroke who receive a CTA. *Materials and Methods*: Single-center, nested, case-control study of patients with ischemic stroke who received a CTA between June 18, 2012 and January 1, 2016. Patients were grouped based on development of CIN. *Findings*: A total of 209 patients were included in the final analysis (178 controls, 31 cases). The prevalence of CIN during the time period studied was 14.8% (95% confidence interval [CI]: 10.2-20.2). A higher proportion of patients who developed CIN had a history of diabetes mellitus (37 [20.56%] versus 15 [48.39%]; $P = .0009$) and reported taking no medications prior to admission (35 [19.44%] versus 11 [35.48%]; $P = .0458$). However, a lower proportion of patients who developed CIN had a history of smoking (59 [32.78] versus 3 [9.68]; $P = .0091$). After statistical adjustment, only a history of diabetes (odds ratio [OR] 4.15 [95% CI: 1.765, 9.754), taking no medications prior to admission (OR 3.56 [95% CI: 1.417, 8.941]) and a self-reported history of smoking (OR 0.204 [95% CI: 0.057, 0.721]) remained associated with the development of CIN. *Conclusions*: Those patients with a history of diabetes mellitus or not taking medications prior to admission should be monitored closely for the development of contrast-induced nephropathy CIN.

Key Words: Stroke—nephropathy—epidemiology—computed tomography angiography—kidney diseases—retrospective

Introduction

Worldwide, stroke is one of the leading causes of morbidity and mortality. Yearly in the United States, approximately 795,000 people have a stroke and 137,000 deaths are attributed to stroke.[1] Rapid identification and treatment of large cerebrovascular occlusions have been shown to improve disability following an ischemic stroke,[2-4] which account for 87% of all stroke cases. The

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Received September 19, 2018; revision received November 2, 2018; accepted November 5, 2018.

Grant Support: None.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.11.012

American Heart Association / American Stroke Association recommend that patients who are being considered for endovascular therapy after experiencing an acute ischemic stroke receive some form of noninvasive intracranial vascular study during their initial evaluation.[5,6] One commonly employed noninvasive intracranial vascular study is computed tomography angiography (CTA). Though CTA is generally well-tolerated, contrast-induced nephropathy (CIN) is a serious adverse event that has been reported in up to 7% of patients who receive contrast for a CTA.[7]

Many factors have been associated with the development of CIN; however, current models for the prediction of CIN are validated primarily in patients who are undergoing coronary angiography.[8] Thus, utility of these models for the prediction of CIN in patients who receive contrast for a CTA is limited. Therefore, the purpose of our study is to evaluate the prevalence of CIN in patients with a presumed diagnosis of ischemic stroke who have undergone CTA and identify risk factors associated with the development of CIN.

Materials and Methods

This was an institutional review board approved, single center, case-control study of patients with stroke-like symptoms who received a CTA. All patients meeting this criterion between June 18, 2012 and January 1, 2016 were screened for inclusion. Patients who had a CTA performed at an outside facility or did not have 3 serum creatinine values within 72 hours of CTA administration were excluded from the analysis. The main outcomes of this study were the period prevalence of CIN in patients who have a presumed diagnosis of ischemic stroke and underwent a CTA and identification of risk factors associated with CIN. Secondary outcomes included determining the effect of CIN on the need for renal replacement therapy and hospital length of stay.

Data Collection

Data collected from the electronic medical record included: age, sex, race, first weight after admission, highest 24-hour systolic blood pressure, highest 24-hour diastolic blood pressure, lowest 24-hour systolic blood pressure, lowest 24-hour diastolic blood pressure, past medical and social history (hypertension, heart failure, diabetes mellitus, hemodialysis, malignancy, vascular disease, liver disease, current smoking status, current alcohol use status, and current illicit drug use status), first reported labs (serum creatinine, serum blood urea nitrogen, serum glucose, hemoglobin, total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides, and serum sodium), home medications (metformin, angiotensin-converting-enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, diuretic, nonsteroidal anti-inflammatory drug, aspirin, lithium, cyclosporine, allopurinol, bisphosphonate, HMG-CoA reductase inhibitor, tacrolimus, and aspirin), total fluid volume administered in the first 24 hours, occurrence of percutaneous angiography, volume of contrast administered during CTA, first reported National Institute of Health Stroke Severity Score, receipt of alteplase, and hospital length of stay. All data were collected and managed using REDCap electronic data capture tools hosted at The University of Tennessee Health Science Center.[9]

Assessment of CIN

CIN was defined as a 0.5 mg/dL or 25% rise from baseline in serum creatinine within 72 hours of CTA. Those patients who met this definition were considered positive. All other included patients were considered controls.

Statistical Analysis

Prevalence was determined as the period prevalence in which the number of cases was divided by the total number of patients included in the study during the specified time period. The exact 95% confidence interval (CI) for the prevalence was estimated. To determine the risk factors associated with CIN, bivariate analyses and multivariate logistic regression were conducted. Continuous variables were assessed for underlying normality through visual inspection of histograms, and Kolmogorov-Smirnov and Shapiro-Wilks tests. In the bivariate analyses, variables with underlying normality were evaluated with Student's t test; however, if the assumption of equal variance was rejected, a Satterthwaite t test was used. Variables that violate the assumption of normality were evaluated with a Mann-Whitney U test. All variables with a P value of less than .15 in the bivariate analysis were included in the initial logistic regression model predicting the development of CIN. Variables were removed in a step-wise fashion from the model based on highest P value. Goodness of fit for each step-wise model was compared with a likelihood ratio test. A variable was considered significant to the model if the likelihood ratio test resulted in a P value of less than .05. To evaluate for significant collinearity or effect modification, we did a bivariate analysis comparing each variable to other variables in the final model. If the comparison resulted in a P value of greater than .05, we determined that no significant collinearity or effect modification was present. In addition, we included an interaction variable between smoking status and history of diabetes. If the interaction variable resulted in a P value of greater than .05, we determined the interaction between smoking status and history of diabetes did not cause effect modification in the model. Thus, we would remove the interaction variable from the model. Also, the goodness of fit for the final model was evaluated with Deviance and Pearson goodness-of-fit tests and the Hosmer and Lemshow goodness-of-fit test.

Table 1. *Demographic information of patients with stroke like symptoms who received a computed tomography angiography*

Variable	Control (n = 180)	Case (n = 31)	*P* value
Age in years *	68.42(14.42)	67.39(12.76)	.71
Male †	79 (43.89)	12 (38.71)	.59
Black or African American ‡	13 (7.22)	5 (16.13)	.15
Race			
White	167 (92.78)	25 (80.65)	-
Black or African American	13 (7.22)	5 (16.13)	-
American Indian or Alaskan Native	0 (0)	1 (3.23)	-
Asian	0 (0)	0 (0)	-
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	-
Weight in kilograms §	80.81(30.01)	82.36(29.16)	.58
Height in inches §	67(6)	67(6)	.86
BMI *	27.86(6.59)	28.59(5.91)	.56
Past medical and social history			
Alcohol use ‡	16 (10.56)	4 (12.9)	.75
Diabetes mellitus †	37 (20.56)	15 (48.39)	<.05
Heart failure ‡	11 (6.11)	4 (12.90)	.26
Hemodialysis ‡	0 (0)	4 (12.90)	<.05
Hypertension †	126 (70)	24 (77.42)	.40
Illicit drug use ‡	5 (2.78)	0(0)	>.99
Liver disease ‡	7 (3.89)	0 (0)	.60
Malignancy ‡	30 (16.67)	4 (12.90)	.79
Smoker †	59 (32.78)	3 (9.68)	.01
Vascular disease †	87 (48.33)	19 (61.29)	.18
None ‡	11 (6.11)	4 (12.90)	.25
Home medications			
ACE inhibitor †	53 (29.44)	7 (22.58)	.43
Angiotensin receptor blocker ‡	19 (10.56)	4 (12.9)	.75
Allopurinol ‡	5 (2.78)	0 (0)	>.99
Aspirin †	82 (45.56)	10 (32.26)	.17
Bisphosphonate	0 (0)	0 (0)	-
Calcium channel blocker †	46 (25.56)	9 (29.03)	.68
Cyclosporine	0 (0)	0 (0)	-
Diuretic †	53 (29.44)	9 (29.03)	.96
Lithium	0 (0)	0 (0)	-
Metformin ‡	17 (9.44)	6 (19.35)	.12
NSAID ‡	17 (9.44)	2 (6.45)	.75
Statin †	82 (45.56)	12 (38.71)	.48
Tacrolimus	0 (0)	0 (0)	-
None †	35 (19.44)	11 (35.48)	.05
First reported BUN in mg/dL §	15(8.5)	16(13)	.57
First reported serum creatinine in mg/dL §	0.935 (0.3)	1(0.6)	.77
BUN: serum creatinine ‖	16.77 (15.84)	17.01 (13.9)	.88
BUN: serum creatinine ≥ 20 †	46 (25.56)	12 (38.71)	.13
Highest 24-hour SBP in mm Hg *	190.5(30.77)	189.3(35.64)	.84
Lowest 24-hour SBP in mm Hg *	112.2 (21.63)	111.9 (22.86)	.96
Highest 24-hour DBP in mm Hg *	103.1 (20.93)	101.2 (21.20)	.64
Lowest 24-hour DBP in mm Hg *	58.71 (10.25)	55.61 (10.95)	.13
Total fluids in milliliters §	1254 (1594)	1497 (1490)	.43
First reported hemoglobin in g/dL *	13.76 (1.82)	13.17 (2.17)	.11
First reported total cholesterol in mg/dL (n = 163, n = 30) §	155 (63)	173 (56)	.05
First reported LDL in mg/dL (n = 162, n = 28) §	85 (56)	91(54)	.24
First reported HDL in mg/dL (n = 163, n = 30) §	39 (20)	42.5 (24)	.52
First reported triglycerides in mg/dL (n = 167, n = 30) §	109 (76)	106.5 (92)	.34
First reported serum sodium in mEq/L §	139 (4)	140 (5)	.57
First reported glucose in mg/dL §	117 (48.5)	131 (86)	.29
CTA contrast volume in milliliters §	70 (0)	70 (0)	.88

(*Continued*)

Table 1 (*Continued*)

Variable	Control (n = 180)	Case (n = 31)	*P* value
Direct angiography ‡	22 (12.22)	4 (12.9)	>.99
First reported NIHSS §	8 (15)	6 (20)	.95
Received alteplase †	39 (21.67)	5 (16.13)	.48

Abbreviation: ACE, Angiotensin Converting Enzyme; BMI, body mass index; BUN, Blood Urea Nitrogen; DBP, Diastolic Blood Pressure; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; NIHSS, National Institute of Health Stroke Scale; NSAID, Non-steroidal anti-inflammatory drug; SBP, systolic blood pressure.

*Mean (standard deviation), *P* value derived from t test.

†n (percent), *P* value derived from chi-square test.

‡n (percent),*P* value derived from Fisher's Exact test.

§Median (interquartile range), *P* value derived from Mann-Whitney U test.

‖Mean (standard deviation), *P* value derived from Satterthwaite t test.

Results

A total of 1609 patients were evaluated for inclusion in the study. Of those evaluated, 211 were included in the final analysis. Full baseline demographics can be seen in Table 1. Patients were excluded for missing data involving variables needed to evaluate for CIN. The overall prevalence of CIN was 14.8% (Exact 95% CI: 10.21%−20.2%). Controls and cases were comparable with respect to age, sex, race, body mass index, and stroke severity. However, a higher proportion of patients who developed CIN had a history of diabetes mellitus (37 [20.56%] versus 15 [48.39%]; *P* = .0009) and reported taking no medications prior to admission (35 [19.44%] versus. 11 [35.48%]; *P* = .0458). However, a lower proportion of patients who developed CIN had a self-reported history of smoking (59 [32.78] versus 3 [9.68]; *P* = .0091).

For our initial logistic regression model, we included lowest diastolic blood pressure in the first 24-hour, admission hemoglobin, a past medical history of diabetes mellitus, self-reported history of smoking, history of taking metformin, report of taking no medications at home, and having a Blood Urea Nitrogen (BUN) to serum creatinine ratio ≥ 20. Though a history of hemodialysis and first reported total cholesterol had *P* values less than .15, we did not include them in the model because there were no patients in the control group with a history of hemodialysis and there was a significant number of patients who did not have a total cholesterol reported during the hospital admission. After a stepwise removal of variables, the final model was significant and contained only a past medical history of diabetes mellitus, self-reported history of smoking, and reporting no medications prior to admission. When controlling for the other variables in the model, a history of diabetes (odds ratio [OR] 4.15; 95% CI: 1.765, 9.75; *P* = .0011) and taking no medications at home (OR 3.56; 95% CI: 1.417, 8.94; *P* = .0069) was associated with an increase in the odds of developing CIN. However, a self-reported history of smoking (OR 0.204; 95% CI: 0.057, 0.72; *P* = .0137) was associated with a decreased risk of developing CIN. There was no effect modification when an interaction variable between smoking and diabetes was included in the final model (*P* > .05), nor was there any significant collinearity detected between the variables in the final model (all *P* > .05). The unadjusted and adjusted OR for variables in the final logistic regression model and model characteristics can be seen in Table 2.

As it relates to secondary outcomes, the development of CIN had no effect of the median hospital length of stay (7 days [6 days] versus 7 days [8 days]; *P* = .3966). In addition, no new renal replacement therapy was required in either group.

Discussion

In our sample of 209 patients with stroke-like symptoms who received a cranial CTA, we found that the prevalence of CIN approached 15%. However, the development of CIN did not result in a need for renal replacement therapy or increased hospital length of stay. In addition, we found that a history of diabetes, no home medications, and a history of smoking were all related to the development of CIN.

In a recent meta-analysis by Brinjiki et al, 14 studies that evaluated the effect of CIN in more than 6000 stroke patients were analyzed. The most common definition of CIN was a 25% rise in serum creatinine. However, the time period of serum creatinine evaluation ranged from unspecified to 5 days. In those patients exposed to contrast, the prevalence of CIN was approximately 3%.[10] Though the prevalence of CIN in our study is higher than observed in the meta-analysis, the frequency of hemodialysis following the development of CIN was comparable to what was observed in the meta-analysis. In the meta-analysis by Brinjiki et al, 0.07% of patients required hemodialysis after developing CIN. In our study, no patients required new hemodialysis. We feel that the inclusion of only those patients with 3 days of serum creatinine values in our study may have artificially elevated the CIN prevalence. With only the sickest patients (ie, those requiring multiple days of laboratory monitoring) included in our study, there is the possibility that the sick person effect

Table 2. *Unadjusted and adjusted odds ratios for variables in the final logistic regression model predicting for the development of contrast induced nephropathy*

Variable	Unadjusted OR	Unadjusted 95% confidence limit	Adjusted OR	Adjusted 95% Wald confidence limits	Estimate	Standard error	Wald chi-square	*P* value
Intercept	-	-	-	-	−2.26	0.34	45.40	<.01
History of diabetes mellitus	3.62	1.64, 8.00	4.15	1.77, 9.75	1.42	0.44	10.65	<.01
No home medications	2.28	1.00, 5.19	3.56	1.42, 8.94	1.27	0.47	7.30	.01
History of smoking	0.22	0.06, 0.75	0.204	0.06, 0.72	−1.59	0.65	6.08	.01

Abbreviation: OR, odds ratio.
Deviance and Pearson $P > .05$ (>.2151 and .0.2384, respectively).
Hosmer and Lemeshow goodness-of-fit $P = .3400$.

could have caused an unusually high number of patients to be diagnosed with CIN in our study.

In our study we found that those patients with a history of diabetes mellitus or those who reported taking no medication at home were more likely to develop CIN. The association of diabetes mellitus and contrast induced nephropathy has been described in many studies;[7,8,11] however, the association of no home medications has not been previously reported. We hypothesize that the lack of home medications is a surrogate marker for a lack of healthcare exposure. Thus, those patients who present with stroke-like symptoms and report no medications at home may have unmeasurable undiagnosed medical conditions that predispose them to the development of CIN. In addition, we found that a history of cigarette smoking was protective. Though the negative effects of tobacco abuse are well-documented, we are not the first to report a protective effect.[12] We are unable to fully explain why smoking was found to be protective in this study. It is well-known that nicotine is a vasoconstrictor and results in transitive decreases in blood supply to organs throughout the body. The kidneys are not exempt to nicotine related decreased blood supply. Thus, smoking may induce a state of remote ischemic preconditioning. Several studies have described the use of remote ischemic preconditioning to reduce the risk of CIN in patients who have undergone percutaneous coronary interventions.[13,14] However, we cannot rule out the possibility that incomplete documentation of smoking status could have led to a misclassification bias in this outcome.

Our study is not without limitations. Because patients with baseline renal insufficiency (ie, creatinine clearance of less than 30 mL/min) are routinely excluded from receiving a CTA at our institution, we are unable to evaluate the effect of a broad range of renal functions on the development of CIN. In addition, as previously discussed, we excluded many patients due to incomplete data. This may have caused a sick person effect in our study, thus, artificially increasing the prevalence of CIN. With any case-control study there is the possibility of selection bias. In our study, cases and controls were selected from the same cohort of patients with stroke-like symptoms who were exposed to contrast; thereby, reducing the risk of selection bias.

Though the prevalence of CIN in our study was relatively high at 14.8%, development of CIN did not adversely affect the clinical outcomes measured in the study. The lack of clinical impact is important when considering the potential benefit from rapid identification of major vessel occultations and thrombectomy. Thus, patients with a history of diabetes or those who do not report home medications should be monitored for the development of CIN; however, such a medical history should not prevent the utilization of CTA in patients with stroke-like symptoms.

Disclosures

Dr. Rowe is on the speaker's bureau for Chiesi and Portula Pharmaceuticals.

All other authors have no disclosures.

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