Contrast Media-Induced Nephropathy in Patients with Unruptured Cerebral Aneurysm After Coiling Endovascular Treatment

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BACKGROUND: **The endovascular coiling procedure to treat cerebral aneurysms using contrast media has become more popular. However, studies of the incidence of, and risk factors for, contrast media-induced nephropathy (CIN) after coiling procedures have been limited. Thus, we evaluated the incidence and risk factors for CIN in patients who had undergone cerebral aneurysmal coiling procedures.**

METHODS: **We retrospectively reviewed the electric medical records of 380 patients who had undergone cerebral aneurysmal coiling treatment under general anesthesia. CIN was defined as an absolute increase in serum creatinine (≥0.5 mg/dL) or a relative increase (≥25%) in the baseline serum creatinine value at 48–72 hours after exposure to a contrast agent.**

RESULTS: **Elective cerebral aneurysmal coiling procedures were performed in 230 patients. Of the 230 patients, CIN developed in 13 (5.6%). The presence of diabetes mellitus (30.8% vs. 9.7%; $P = 0.040$) and patient age >75 years (30.8% vs. 6.5%; $P = 0.012$) were risk factors for CIN.**

CONCLUSIONS: **Our study has demonstrated that the incidence of CIN in patients undergoing elective cerebral aneurysmal coiling procedures is ~6.0%. We also identified underlying diabetes mellitus and advanced age (≥75 years) as potential risk factors.**

INTRODUCTION

Contrast media-induced nephropathy (CIN) is a well-known potential complication of angiography. Many studies have shown that the use of contrast media increases the incidence of CIN in patients undergoing percutaneous coronary intervention (PCI). The incidence of CIN across low-risk populations has been estimated to be 3%–6%.[1,2] However, in high-risk populations, its incidence can approach 20%–30%.[3] Therefore, the risk assessment for CIN is important. In the general population, some risk factors, such as chronic renal disease, diabetes, and cardiovascular disease, have been identified.[4-10] In addition, only a small number of studies have assessed the incidence of CIN in neurological patients undergoing radiological studies using contrast media. Most of these studies included patients with ischemic stroke.[11-14] Despite preventative strategies, including adequate hydration and administration of N-acetylcysteine,[15,16] CIN remains the third most common cause of hospital-acquired renal failure. Thus, we investigated the incidence of, risk factors for, efficacy of preventive measures for, and morbidity of CIN after the use of contrast media in patients who had undergone interventional coiling procedures for cerebral aneurysms.

METHODS

Patient Selection and Study Design

We retrospectively reviewed the electronic medical records of 380 patients who had undergone cerebral aneurysmal coiling treatment under general anesthesia from January 2009 to September 2015 at 2 referral hospitals in Korea. Of these 380 patients, 233 had

Key words
- Cerebral angiography
- Contrast media
- Intracranial aneurysm
- Nephropathy

Abbreviations and Acronyms
CIN: Contrast media-induced nephropathy
GFR: Glomerular filtration rate
MACD: Maximum allowable contrast dose
PCI: Percutaneous coronary intervention

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had unruptured aneurysms and 157 had ruptured aneurysms. Those patients who had undergone craniectomy were excluded. Thus, we analyzed the data from 230 patients with unruptured aneurysms. The ethics review committee and institutional review board of each hospital approved the study protocol (approval numbers, OC13RASI0126 and UC15RAMI0086).

CIN Definition

We defined and graded CIN according to the study by Harjai et al.[17] A serum creatinine increase <25% greater than baseline and <0.5 mg/dL greater than baseline was categorized as grade 0. A serum creatinine increase of ≥25% greater than baseline and <0.5 mg/dL greater than baseline was categorized as grade 1. Finally, a serum creatinine increase of ≥0.5 mg/dL greater than baseline was categorized as grade 2. To exclude renal failure from causes other than CIN, those patients with no data available on the serum creatinine level within 1 week after aneurysmal coiling, those with no data available on the serum creatinine level before aneurysmal coiling, those who had previously undergone maintenance dialysis at the procedure, those with severely decompensated heart function (Killip class IV) to exclude the prerenal factor,[18] and those aged <15 years were excluded.

Renal Function

The estimated glomerular filtration rate (GFR) was determined using the abbreviated Cockcroft-Gault equation: (140 − age) × lean body weight [kg])/(creatinine [mg/dL] × 72 × (0.85 if female). Anemia was defined by the hematocrit level (<39% for men and <36% for women). Chronic renal failure was defined as decreased kidney function shown by a GFR of <60 mL/min per 1.73 m^2 or markers of kidney damage, or both, of at least 3 months' duration, regardless of the underlying cause.[19]

Coiling Procedure and Treatment Protocol

Experienced neurointerventionalists chose the type of procedure (e.g., endovascular coiling procedure, extraventricular drainage, craniotomy, craniectomy, and/or aneurysmal clipping with craniotomy) according to the patient's physical status. Patients with an unruptured aneurysm without symptoms were discharged and returned to the hospital to undergo an elective cerebral aneurysmal coiling procedure 1 or 2 weeks after presentation. Cerebral coil embolization was performed with the patient under general anesthesia. The patients who had undergone ≥1 contrast-enhanced radiological study (e.g., computed tomographic angiography, computed tomographic perfusion, diagnostic angiography, cerebral coil embolization) were included. The contrast media used were iohexol (Iobrix; Taejoon Pharmaceutical Co., Seoul, Korea) 350 mOsm/kg, iopromide (Ultravist; Bayer Healthcare, Berlin, Germany) 428 mOsm/kg, or ioversol (Optiray; Mallinckrodt Pharmaceuticals, St. Louis, Missouri, USA) 702 mOsm/kg for computed tomographic angiography or computed tomographic perfusion. All the agents were nonionic low-osmolar agents. For diagnostic angiography and coil embolization, iodixanol-320 (Visipaque; General Electric Healthcare, Princeton, New Jersey, USA) 290 mOsm/kg was used (a nonionic iso-osmolar agent). All the contrast medium agents were used by specialized neurointerventionalists with the same protocol. The contrast volume used during diagnostic angiography within 48 hours before the coiling procedure and that used during the coiling procedure were summed as the cumulative dose of contrast media used. The maximum allowable contrast dose (MACD) was calculated for each patient using the ideal body weight and baseline serum creatinine value with the following formula: 5 × ideal body weight/baseline creatinine.[20] In-hospital mortality was also analyzed.

All patients received intravenous hydration with an isotonic solution at a rate of 1–1.5 mL/kg periprocedurally. N-acetylcysteine was administered intravenously or orally for high-risk patients who had risk factors for CIN such as chronic renal failure, diabetes mellitus, heart failure, emergency procedure, and older age. The dose used was 150–300 mg/kg, and the duration was 3 or 4 days. After the procedure, all the patients were transferred to the intensive care unit for ≥24 hours. Some patients underwent postoperative contrast-enhanced computed tomography.

Statistical Analysis

Because of the nontrivial amount of missing outcomes data, an imputation model was created, which contained variables that were related to the missing data or outcome measure.[21] To determine whether the missing data were missing at random, we evaluated the correlation between the missing variables and the other variables included in the multivariable model. No significant correlation was found for most of the variables, supporting the finding that the missing data were missing at random. Therefore, we used multiple imputation procedures and the Markov Chain Monte Carlo method to establish the imputed data set ($n = 5$) and, accordingly, the pooled data set.

Data for descriptive statistics are presented as frequencies for categorical variables and the parameter of distribution (mean). Comparisons of continuous variables were performed using independent-sample t tests (Mann-Whitney U test for nonparametric variables). Comparisons of categorical data were performed using the χ^2 test or Fisher exact test. The risk factors for CIN in patients with an unruptured aneurysm or a ruptured aneurysm ($n = 380$) were analyzed using the binary logistic regression model (multivariate analysis). Statistical significance was considered present at $P \leq 0.05$. All analyses were performed using the IBM SPSS statistics, version 20 (IBM Corp., Armonk, New York, USA).

RESULTS

All 230 patients with an unruptured aneurysm had undergone elective neurointerventional treatment. The demographic data and clinical characteristics of the patients with an unruptured aneurysm are listed in **Table 1**. Of the 230 patients, 13 developed CIN (5.6%). Of the 13 episodes of CIN, 11 were categorized as grade 1, and 2 were categorized as grade 2. Of the 230 patients, 25 had diabetes mellitus and 18 were aged >75 years. The patients aged >75 years developed CIN more than the rest of the population (30.8% vs. 6.5%; $P = 0.012$). The patients with underlying diabetes mellitus also developed CIN more often than the rest of the population (30.8% vs. 9.7%; $P = 0.040$). The distribution of gender, contrast allergy history, perioperative

Table 1. Clinical Characteristics ($n = 230$)

Characteristic	CIN ($n = 13$)	No CIN ($n = 217$)	*P* Value
Age (years)	66.7 ± 10.8	56.4 ± 12.3	0.004
Age ≥75 years	4 (30.8)	14 (6.5)	0.012
Male gender	3 (23.1)	56 (25.8)	>0.999
History of contrast allergy	0 (0.0)	2 (0.9)	>0.999
Previous use of agents affecting kidney function			
NSAIDs	7 (53.8)	102 (47.0)	0.631
Angiotensin-receptor blocking agents	3 (23.1)	34 (15.7)	0.445
Preoperative data			
Basal eGFR (mL/min/1.73 m^2)	100.7 ± 50.4	89.9 ± 29.6	0.456
eGFR <90 mL/min/1.73 m^2	5 (38.5)	113 (54.8)	0.250
Hematocrit (%)	37.4 ± 3.7	39.0 ± 3.5	0.165
Anemia	3 (23.1)	27 (12.4)	0.232
Concurrent extraventricular drainage	2 (15.4)	6 (2.8)	0.068
Underlying comorbidity			
Hypertension	7 (53.8)	90 (41.5)	0.380
Diabetes mellitus	4 (30.8)	21 (9.7)	0.040
Chronic renal failure	1 (7.7)	1 (0.5)	0.110
Dyslipidemia	2 (15.4)	17 (7.8)	0.292
Coronary arterial disease	1 (7.7)	10 (4.6)	0.480
Associated CVA	2 (15.4)	10 (4.6)	0.141
Previous cerebral aneurysm clipping	1 (7.7)	6 (2.8)	0.338

Data presented as mean ± standard deviation or *n* (%).
CIN, contrast media-induced nephropathy (absolute serum creatinine increase of ≥0.5 mg/dL or relative increase of ≥25% from baseline serum creatinine value 48–72 hours after exposure to contrast agents in accordance with Harjai et al.[17]); NSAIDs, nonsteroidal anti-inflammatory drugs; eGFR, estimated glomerular filtration rate; CVA, cerebrovascular accident.

use of agents affecting kidney function, basal GFR, hematocrit, anemia, extraventricular drainage, hypertension, chronic kidney disease, dyslipidemia, coronary artery disease, associated cerebrovascular accident, and previous aneurysm clipping was comparable between the patients with and without CIN, without statistically significant differences (Table 1). The operative time, amount of administered fluid, urine output, fluid balance, prophylactic use of N-acetylcysteine, use of inotropic agents, anesthetic agents used, emergency procedure, and fluid balance within 24 hours also were not statistically significant risk factors for the development of CIN (Table 2).

Data on the factors associated with contrast use and CIN are listed in Table 3. The cumulative dose of contrast media was 226.9 ± 59.9 mL in the patients with CIN and 206.4 ± 57.2 mL in those without CIN (P = 0.212). Eight patients had received a volume exceeding the MACD. Of the 8 patients who had received a volume exceeding the MACD, 2 developed CIN. However, the difference was not statistically significant (15.4% vs. 2.8%; P = 0.068). In our study, the significant risk factors for CIN were age ≥75 years and diabetes mellitus on univariate analyses.

In-hospital mortality occurred in no patients (0%; 4 of 230). Of the 13 patients with CIN, 1 developed pulmonary edema and required continuous furosemide infusion but returned to the baseline creatinine level without hemodialysis. All 13 patients with CIN returned to their baseline creatinine level.

DISCUSSION

CIN is a well-known complication of radiological interventional treatment. In patients undergoing neurointerventions for acute ischemic stroke, the incidence of CIN has been reported to be 2%–3%.[12,14] For patients undergoing treatment of subarachnoid hemorrhage, relatively small studies have reported an incidence of 2.9%–3.9%.[22,23] However, data only from patients with an unruptured cerebral aneurysm undergoing an elective coiling procedure are lacking. The aim of the present study was to estimate the incidence of and risk factors for CIN in patients with an unruptured aneurysm undergoing a neuroendovascular intervention for the first time.

Our data have shown that the incidence of CIN among patients undergoing an elective neurointervention was 5.6% (13 of 230

Table 2. Perioperative Data ($n = 230$)

Variable	CIN ($n = 13$)	No CIN (n = 217)	*P* Value
Intraoperative data			
Operation time (minutes)	151.5 ± 67.8	142.9 ± 48.0	0.539
Fluid administered (mL)			
Total	919.2 ± 675.6	1025.6 ± 635.7	0.560
Colloid fluid	169.2 ± 204.7	159.8 ± 205.5	0.872
Urine output	601.2 ± 910.5	558.0 ± 518.9	0.868
Fluid balance	366.4 ± 681.0	522.0 ± 505.8	0.292
Prophylactic use of NAC	8 (61.5)	135 (62.2)	>0.999
Use of inotropic agents	0 (0.0)	5 (2.3)	>0.999
Anesthetic agents			
TIVA	3 (23.1)	53 (24.4)	
Desflurane	5 (38.5)	41 (18.9)	
Sevoflurane	5 (38.5)	123 (56.7)	
Emergency procedure	2 (15.4)	17 (7.8)	0.292
Postoperative fluid balance within 24 hours	467.6 ± 800.08	314.2 ± 842.2	0.523

Data presented as mean ± standard deviation or *n* (%).
CIN, contrast media-induced nephropathy (absolute serum creatinine increase of ≥0.5 mg/dL or relative increase of ≥25% from baseline serum creatinine value 48–72 hours after exposure to contrast agents in accordance with Harjai et al.[17]); NAC, *N*-acetylcysteine; TIVA, total intravenous anesthesia.

patients) using the definition of Harjai et al.[17] Of the 13 episodes, 11 were categorized as grade 1, and 2 were categorized as grade 2. This result is comparable to that in the general population.[2,11,14,24] However, the incidence was much lower than the reported incidence of 20%–30% in high-risk patients undergoing PCIs, which can be attributed to patients with severe comorbidities undergoing PCI compared with patients with cerebral aneurysms.

Some studies have shown that the incidence of CIN in patients receiving a contrast agent in volumes exceeding the MACD during cardiovascular procedures will be greater than that in those whose MACD was not exceeded. Hence, the MACD has been reported as an independent risk factor for CIN.[20,25] In our study, we found tendency for patients who had received a volume exceeding the MACD to develop CIN more often than the patients who had received a volume not exceeding the MACD (15.4% vs. 2.8%; P = 0.068). However, the difference was not statistically significant, because only 8 of the 230 patients who had undergone an elective aneurysmal coiling procedure (3.5%)

Table 3. Factors Associated with Contrast Use ($n = 230$)

Variable	CIN ($n = 13$)	No CIN ($n = 217$)	*P* Value
Preoperative data			
Computed tomography using contrast agent	3 (23.1)	24 (11.1)	0.185
Diagnostic angiography within previous 48 hours	5 (38.5)	60 (27.6)	0.526
Postoperative data			
Computed tomography using contrast agent	7 (53.8)	70 (32.3)	0.133
Cumulative dose of contrast media (mL)	226.9 ± 59.9	206.4 ± 57.2	0.212
Cumulative dose of contrast media ≥250 mL	5 (38.5)	53 (24.4)	0.322
Contrast media volume exceeding MACD	2 (15.4)	6 (2.8)	0.068

Data presented as *n* (%) or mean ± standard deviation.
CIN, contrast media-induced nephropathy (absolute serum creatinine increase of ≥0.5 mg/dL or relative increase of ≥25% from baseline serum creatinine value 48–72 hours after exposure to contrast agents in accordance with Harjai et al.[17]); MACD, maximum allowable contrast dose.

received a volume exceeding the MACD and only 2 of these 8 patients had developed CIN.

One study reported that a contrast dose of ≥250 mL can increase the incidence of CIN.[13] We analyzed the cumulative dose, rather than a single dose of contrast medium, and found that the incidence of CIN in patients with a cumulative contrast dose of ≥250 mL for 48 hours after exposure to the contrast agent was 8.6% (5 of 58 patients).

Diabetes mellitus was identified as an important predisposing factor for the development of CIN, especially in patients with renal functional impairment. The diabetic kidney is susceptible to intensified hypoxic and oxidative stress after administration of a contrast agent.[26] Our results correspond with the findings of previous studies, which reported that the presence of diabetes mellitus was a risk factor for CIN after aneurysmal coiling (Table 1).

In a retrospective analysis of the Mayo Clinic PCI registry, for patients with a baseline creatinine <2.0 mg/dL, the risk of CIN was greater among the patients with diabetes mellitus. In contrast, in patients with a baseline creatinine >2.0 mg/dL, both patients and without diabetes had a significant risk of acute renal failure.[9] In our study, patients with underlying chronic renal failure developed CIN more often; however the difference was not statistically significant (7.7% vs. 0.5%; P = 0.110) because the number of patients with CIN was small (2 of 230).

Many studies have reported on the prophylactic use of N-acetylcysteine.[27,28] The use of N-acetylcysteine is common and steadily increased during the study period. Our study did not have a standardized protocol for the use of N-acetylcysteine, and N-acetylcysteine use was more frequent in critically ill patients at risk of developing CIN (Table 2). Hence, we could not prove the efficacy and safety of N-acetylcysteine. Another limitation of our study was its retrospective nature. Larger prospective studies are needed to identify the incidence and risk factors for CIN in patients undergoing neurointervention.

CONCLUSIONS

In our study, the incidence of CIN in patients who underwent a coiling procedure for an unruptured cerebral aneurysmal was 5.6%. The risk of CIN might be increased for patients with underlying diabetes mellitus and older patients (age, ≥75 years). Therefore, a careful evaluation of each patient scheduled to undergo a coiling procedure for a cerebral aneurysm under general anesthesia is essential to determine the presence of risk factors.

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