original article

Predictive factors for contrast-induced acute kidney injury in high-risk patients given N-acetylcysteine prophylaxis

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BACKGROUND: Contrast–induced acute kidney injury (CI-AKI) is recognized as a common complication of radiographic contrast-enhanced procedures. N-acetylcysteine (NAC) is commonly prescribed, but CI-AKI can still develop despite NAC administration as prophylaxis.

OBJECTIVE: Identify the predictive factors for development of CI-AKI in patients prescribed NAC.

DESIGN: Prospective, cross-sectional.

SETTING: A tertiary hospital in Malaysia.

PATIENTS AND METHODS: All adult patients who were prescribed NAC for prevention of CI-AKI were identified through an NAC drug usage monitoring card maintained by the inpatient pharmacy. The study was conducted from March to July 2017.

MAIN OUTCOME MEASURES: Statistically significant predictive factors for development of CI-AKI despite NAC administration.

SAMPLE SIZE: 152

RESULTS: The most commonly recognized risk factors for CI-AKI present in the study population were renal impairment (n=131, 86.2%), anemia (n=107, 70.4%), and diabetes mellitus (n=90, 59.2%). Hydration therapy was initiated in 128 patients (84.2%) prior to the contrast-enhanced procedure. Sixty-one (40.1%) were treated with nephrotoxic medications concomitantly with NAC. Fifteen (9.9%) patients developed AKI. Hypotension (OR: 6.02; 95% CI 1.25-28.97) and use of high contrast volume (OR: 6.56; 95% CI: 1.41-30.64) significantly increased the odds for AKI. Prior hydration therapy (OR: 0.13; 95% CI 0.03-0.59) showed protective effects.

CONCLUSION: The risk predictors identified for CI-AKI were hypotension, high contrast volume and prior hydration therapy.

LIMITATION: May not have identified other confounding factors for development of CI-AKI.

CONFLICT OF INTEREST: None.

Contrast–induced acute kidney injury (CI-AKI), formerly known as contrast-induced nephropathy (CIN) is recognised as a common complication of radiographic contrast-enhanced procedures.[1] CI-AKI was reported to be the third leading cause of acute kidney injury (AKI) in hospitalized patients after renal hypoperfusion and nephrotoxic medication use.[2] CI-AKI is defined as an abrupt decline in kidney function after an exposure to iodinated contrast media that is not attributable to other etiologies.[1] A more specific and widely used definition of CI-AKI has been a rise in serum creatinine (SCr) concentration by 25% or 44 µmol/L from the baseline value within 48 hours after administration of contrast media.[3,4] The overall prevalence of CI-AKI has been estimated as approximately 2%, with the prevalence increasing to more than 30% in the presence of risk factors such as pre-existing renal impairment, or diabetes mellitus.[5,6]

The pathophysiology of CI-AKI is not completely understood. Postulated mechanisms for CI-AKI are cell damage caused by direct cytotoxic effect of contrast to renal tubular epithelial cells, renal vasoconstriction leading to medullary ischemia, and the formation of free reactive oxygen species.[1] The presence of contrast media within tubular epithelial cells increases the viscosity of tubular fluid, impeding its flow, which leads to further renal retention and cytotoxic exposure to renal cells.[7] The mainstay for CI-AKI prevention remains hydration.[3] Intravenous hydration at an infusion rate of 1-1.5 mL/kg/hour for at least 6 hours pre- and post-contrast media administration is recommended for patients with high-risk for CI-AKI.[8]

CI-AKI has been reported to cause an increased risk of morbidity including need for dialysis, prolonged hospital stay, cardiovascular events as well as mortality.[9] With the rapidly aging global population and increasing number of patients with comorbidities such as diabetes mellitus, renal impairment, the increasing use of contrast-mediated diagnostic and intervention procedures will probably increase the prevalence of CI-AKI in the future.[6] N-acetylcysteine (NAC) was postulated to have a protective effect against contrast media owing to its antioxidant and vasodilatory properties.[10] However, for the last decade, multiple studies including meta-analyses and systematic reviews have had conflicting results on the efficacy of NAC, and therefore the efficacy is uncertain.[11,12] Despite the low level of the evidence for the efficacy of NAC against CI-AKI, NAC is recommended because it is generally well tolerated, inexpensive and relatively safe.[8] In Malaysia, there is no national standard guideline on CI-AKI prevention. The approved indication of NAC by the Ministry of Health Malaysia is only for paracetamol poisoning. Despite being easy to use, well-tolerated and inexpensive, off-label use of NAC is common in local settings and requires special approval. The intention of this study was to gain a better understanding of the utilization pattern of NAC in the prevention of CI-AKI in a local setting. Information on predictive factors associated with the occurrence of CI-AKI despite use of NAC will be useful in predicting the likelihood of CI-AKI and help in the implementation of extra precautionary steps in managing patients. The specific aim of this study was to identify the predictive factors for development of CI-AKI despite prophylactic NAC administration.

PATIENTS AND METHODS

This was a prospective study conducted in all inpatient wards at Universiti Kebangsaan Malaysia Medical Centre, Malaysia. All adult patients who were prescribed NAC for CI-AKI prevention were identified through an NAC drug usage monitoring card maintained by the inpatient pharmacy. Eligible patients were recruited into the study based on the following inclusive criteria: age 18 years or older with inpatient status who had been prescribed with NAC for CI-AKI prevention at the time of the study. Patients who had incomplete medical records for data collection during the study period were excluded. The data collection was carried out over a period of 5 months from March 2017 to July 2017.

The data collected included demographic characteristics such as age, gender, race, weight, height, body mass index (BMI), diagnosis and concomitant medications. Additional data including use of IV hydration, concomitant use of nephrotoxic agents, type of NAC regimen, prescriber's specialty, type of imaging procedure, type of contrast use, volume of contrast, serum creatinine levels pre- and post- contrast procedure were also collected. These and other potential risk factors for CI-AKI development were subsequently assessed. The risk factors listed in the Mehran Simple Risk Score for prevention of CI-AKI were used a reference in data collection.[3] Potential risk factors were categorized as patient-related, procedure-related, and contrast-related. The patient-related factors included renal impairment, advanced age, hypotension (SBP ≤90 mm Hg), congestive heart failure (ejection fraction <40%), diabetes mellitus, and anemia (baseline hematocrit <39% in men, <36% in women). Procedure-related risk factors were coronary angiography/angioplasty and renal angiogram/angioplasty. The contrast-related factors included exposure to large volume of contrast media (≥150 mL), and use of high osmolarity contrast. For intravenous hydration use, patients were further cat-

egorized into two groups; first group received intravenous hydration solution including IV normal saline, IV sodium bicarbonate fluids, or IV dextrose saline within 24 hours prior to radiocontrast imaging procedure and the second group did not receive intravenous hydration solution. Concomitant medications were defined as all concurrent medications that were taken by the patient during the administration of NAC for CI-AKI prevention. Patients who developed CI-AKI despite administration of NAC were further analyzed to determine predictive factors possibly associated with CI-AKI development. Ethics approval was obtained from the Universiti Kebangsaan Malaysia (UKM) Research Ethic Committee prior to the commencement of the study (UKM PPI/111/8/JEP-2016-724).

All statistical analysis was performed using IBM SPSS version 21.0 (Armonk, New York). Descriptive statistics were used to analyse demographic data, risk factors for CI-AKI and other utilization patterns of NAC. Chi-squared analysis was performed to analyze the association of risk factors with the occurrence of CI-AKI. Univariate and multivariate analysis were performed using multiple logistic regression to identify predictive factors for the development of CI-AKI prevalence despite NAC administration. Factors with a probability value of less than 0.20 in the univariate analysis were included in the multivariate analysis. A *P* values of <.05 denoted statistical significance and confidence interval of 95% are provided.

RESULTS

During the 5-month period, 169 patients were prescribed with NAC for the prevention of CI-AKI. Fifteen patients were excluded due to incomplete laboratory data. Two more patients were excluded because they missed the appointments, leaving 152 patients (**Table 1**). All patients were followed up for at least 48 hours or until patient discharge if less than 48 hours post-contrast administration. The majority of patients were male (72.4%) with a median (interquartile range) age of 68 (61-75) years. Just over half (56.0%) had a normal body mass-index (BMI) which corresponded to the median BMI of 24.7 (21.9-27.1) kg/m^2, followed by 31.6% and 13.8% in overweight and obese category, respectively. The majority of the patients were classified as having stage 3B moderately reduced kidney function (31.6%). The median initial serum creatinine of the patients was 154 (117-209) µmol/L, and the median estimated glomerular filtration rate (eGFR) was 38 (24.8-50.5) mL/min/1.73 m^2. The three most common concomitant medications administered by patients while receiving NAC were statins (49.3%), calcium channel blockers

Table 1. Demographic and clinical characteristics (n=152).

Characteristics	n (%)
Gender	
Male	110 (72.4)
Female	42 (27.6)
Ethnic group	
Malay	80 (52.6)
Chinese	61 (40.1)
Indian	11 (7.2)
Age, years (median, IQR)	68 (61-75)
Body mass index, kg/m^2 (median, IQR)	24.7 (21.9-27.1)
Body mass index by category	
Underweight	7 (4.6)
Normal	76 (50.0)
Overweight	48 (31.6)
Obese	21 (13.8)
Initial serum creatinine, µmol (median, IQR)	154 (117-216)
Initial eGFR, mL/min/1.73 m^2 (median, IQR)	38 (24.8-50.5)
Initial eGFR by KDOQI staging, mL/min/1.73 m^2	
>90	5 (3.3)
60-89	16 (10.5)
45-59	29 (19.1)
30-44	48 (31.6)
15-29	34 (22.4)
<15	20 (13.2)
Concomitant medications	
ACE/ARB	29 (19.1)
Antiplatelet	56 (36.8)
Diuretic	38 (25)
Beta-blocker	47 (30.9)
CCB	66 (43.4)
Statin	75 (49.3)
Oral hypoglycemic agents	28 (18.4)
Antibiotics	65 (42.8)
NSAIDs	4 (2.6)

eGFR: estimated glomerular filtration rate; ACE/ARB: angiotensin-converting enzyme-inhibitor/angiotensin-receptor blocker; CCB: calcium channel blocker; NSAIDs: non-steroidal anti-inflammatory drugs; KDOQI: Kidney Disease Outcomes Quality Initiative

(43.4%) and antibiotics (42.8%).

The NAC regimen used in this study was as follows: in non-urgent/elective cases, oral NAC 1200 mg twice daily was given starting one day before the procedure and continued for 2 days after the procedure. In urgent cases, oral NAC 1200 mg was given stat or after the procedure and twice daily for 2 days. Patients were categorised into whether they had or had not received any form of intravenous hydration solution within 24 hours prior to radiocontrast imaging procedure. Based on observed practice, the majority were given with normal saline 0.9%, ranging 500 mL-1000 mL over 24 hours based on hydration status.

The top three risk factors for CI-AKI were renal impairment (86.2%), anemia (70.4%), and diabetes mellitus (59.2%) (**Table 2**). Other risk factors were advanced age ≥75 (25%), having undergone coronary angiogram/angioplasty (16.4%), use of high contrast volume of ≥150 mL (11.8%) and congestive cardiac failure (11.2%). Twelve (7.9%) patients had hypotension with systolic blood pressure ≤90 mm Hg. No patients were given high osmolarity contrast media. Sixty-one (40.1%) were taking concomitant nephrotoxic medications including an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, biguanide, and diuretics.

Most patients at high risk for CI-AKI were prescribed NAC as prophylaxis and there was a high rate of adherence (95.4%). Hydration therapy was used in 128 (83.1%) patients prior to the contrast-enhanced procedure. Sixty-one (40.1%) were treated with nephrotoxic medications concomitantly. Oral NAC (1200 mg twice daily 1 day before the procedure and 1200 mg twice daily for 2 days after the procedure) was the primary route used in the prevention of CI-AKI (98.7%), with only 2 cases (1.3%) being given intravenous NAC due to inability to take orally (**Table 3**). Most underwent a computed tomography scan (112, 73.7%), while 25 (16.4%) underwent a coronary angiogram/angioplasty. All iodinated contrast-enhanced procedures used low-osmolarity contrast media (97.4%). There were 4 cases (2.6%) of gadolinium-based contrast use which was consistent with the 4 cases of magnetic resonance imaging (MRI). The contrast volume was kept at a low volume, with 85.5% less than 150 mL versus 11.8% with equal or more than 150 mL. For MRI cases, the gadolinium contrast volume was kept at a standard dose of 0.1 mmol/kg, which corresponded to <20 mL.

Fifteen patients (9.9%) had acute kidney injury after the procedure while 100 (65.8%) patients had stable renal function. Of the 152 patients, 17.1% of patients did not have their serum creatinine level repeated after the procedure. Ten (6.6%) patients were on regular dialysis

Table 2. Risk factors for contrast–induced acute kidney injury.

	n (%)
Risk factors for CI-AKI	
Renal impairment	131 (86.2)
Age ≥75 years	38 (25.0)
Hypotension	12 (7.9)
Congestive cardiac failure	17 (11.2)
Diabetes mellitus	90 (59.2)
Anemia	107 (70.4)
Coronary angiogram/ angioplasty	25 (16.4)
Renal angiogram/angioplasty	2 (1.3)
High contrast volume	18 (11.8)
High osmolarity contrast media	0 (0)
Prior hydration therapy	
Yes	128 (84.2)
No	24 (15.8)
Concomitant nephrotoxic agents	
Yes	61 (40.1)
No	91 (59.9)

prior to contrast procedures, which raised the question of the necessity of NAC prescription. Univariate analysis showed that hypotension (χ^2=5.83; *P*=.016), high contrast volume (χ^2= 7.22; *P*=.007), and prior hydration therapy (χ^2=9.68; *P*=.002) were significantly associated with the development of CI-AKI (**Table 4**). Gender (χ^2=3.79; *P*=.052) and diabetes mellitus (χ^2=2.65; *P*=.104) were also included in the multivariate analysis. Anemia showed a probability of >0.20 in the univariate test, therefore was not included in multivariate analysis. The multivariate analysis (**Table 5**) demonstrated that hypotension (OR: 6.02; 95% CI 1.25-28.97) and use of high contrast volume (OR: 6.56; 95% CI: 1.41-30.64) significantly increased the odds for the presence of AKI. Prior hydration therapy (OR: 0.13; 95% CI 0.03-0.59) showed protective effects on AKI development.

DISCUSSION

As the prerequisite criteria for NAC prescription was the presence of risk factors for CI-AKI, it was not surprising that the majority of the patients in this study had underlying chronic kidney disease. The baseline creatinine and eGRF were similar to those reported in a multicen-

Table 3. N-acetylcysteine utilization pattern and patient outcome.

Variable	n (%)
Type of NAC regimen	
Oral	150 (98.7)
Intravenous	2 (1.3)
Prescriber speciality	
Internal Medicine	42 (27.6)
Surgical	34 (22.4)
Cardiology	28 (18.4)
Urology	20 (13.2)
Nephrology	9 (5.9)
Orthopedic	7 (4.6)
Others	12 (7.9)
Type of procedure	
Computed tomography	112 (73.7)
Coronary angiogram/angioplasty	25 (16.4)
Digital subtraction angioplasty	6 (3.9)
Magnetic resonance imaging	4 (2.6)
Renal angiogram/angioplasty	2 (1.3)
Others	3 (2.0)
Type of contrast	
High-osmolarity contrast media	0 (0)
Iso-osmolarity contrast media	0 (0)
Low-osmolarity contrast media	148 (97.4)
Gadolinium-based	4 (2.6)
Iodinated contrast volume	
>150 mL	18 (11.8)
<150 mL	130 (85.5)
Patient outcome	
No acute kidney injury	100 (65.8)
No follow-up serum creatinine	26 (17.1)
Acute kidney injury	15 (9.9)
On regular dialysis	10 (6.6)
Death	1 (0.7)

Table 4. Univariate analysis of risk factors for development of contrast-induced acute kidney injury.

Variable		Developed CI-AKI (n=15)	Did not develop CI-AKI (n=100)	P value [χ^2 (df)]
Gender	Male	8 (53.3)	77 (77)	.052 [3.79 (1)]
	Female	7 (46.7)	23 (23)	
Body mass index		25.4 (3.5)	24.3 (5.3)	.28
Age		72.0 (14)	67 (13)	.55
Initial eGFR, mL/min/1.73m^2	>90	0 (0)	3(3)	.859 [1.93 (5)]
	60-89	1 (6.7)	12 (12)	
	45-59	4 (26.7)	19 (19)	
	30-44	4 (26.7)	35 (35)	
	15-29	4 (26.7)	23 (23)	
	<15	2 (13.3)	8 (8)	
Renal impairment	Yes	14 (93.3)	85 (85)	.385 [0.756 (1)]
	No	1 (6.7)	15 (15)	
Hypotension	Yes	14 (93.3)	7 (7)	.016* [5.832 (1)]
	No	11 (73.3)	93 (93)	
Congestive cardiac failure	Yes	3 (20)	10 (10)	.254 [1.301 (1)]
	No	12 (80)	90 (90)	
Diabetes mellitus	Yes	12 (80)	58 (58)	.104 [2.650 (1)]
	No	3 (20)	42 (42)	
Anemia	Yes	9 (60)	72 (72)	.342 [0.902 (1)]
	No	6 (40)	28 (28)	
Coronary angiogram/ angioplasty	Yes	4 (26.7)	17 (17)	.366 [0.817 (1)]
	No	11 (73.3)	83 (83)	
High contrast volume	Yes	5 (33.3)	9 (9)	.007* [7.223 (1)]
	No	10 (66.7)	91 (91)	
Prior hydration therapy	Yes	10 (66.7)	93 (93)	.002* [9.678 (1)]
	No	5 (33.3)	7 (7)	
Concomitant nephrotoxic agents	Yes	5 (33.3)	39 (39)	.674 [0.177 (1)]
	No	10 (66.7)	61 (61)	

Values are n (%). Statistical comparisons by chi-squared (or Fisher exact test as appropriate) for categorical variables or Mann-Whitney test for continuous variables. eGFR: estimated glomerular filtration rate.

Table 5. Multiple logistic regression model for predictors of development of contrast-induced acute kidney injury after receiving contrast media.

Variable	B	*P* value	Adjusted odds ratio	95% CI
Male gender	-.971	.141	0.379	0.10-1.38
Hypotension	1.795	.025	6.019	1.25-28.97
Diabetes mellitus	.596	.428	1.815	0.42-7.92
High contrast volume	1.882	.017	6.564	1.41-30.64
Prior Hydration therapy	-2.042	.008	0.130	0.03-.59

Omnibus Test of Model Coefficients: *P*<.001; Hosmer and Lemeshow test χ^2=4.234, df=5 , *P*=.516. -2 Log likelihood 67.589, Cox&Snell R square 0.170, Nagelkerke R square 0.316

tre, randomized controlled study assessing CI-AKI prevention using NAC plus sodium bicarbonate in Asian countries.[13] Further, stratification based on National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) CKD stages showed that the majority of patients had moderately reduced kidney function. This may have implied a higher risk for CI-AKI as the risk for CI-AKI is significantly increased in renally impaired patients and the risk rises proportionally to the severity of existing renal impairment.[14] Among all concomitant medications taken by patients in this study, a cholesterol-lowering statin appeared to be the most common concomitant medication. This was not surprising as the majority of patients in this study were older, with comorbidities such as cardiovascular, diabetes mellitus or dyslipidemia. Statins have had a renoprotective effect against CI-AKI development in numerous observational and randomised studies.[5] A significant improvement in CI-AKI incidence was observed in the statin group versus control group (6.7% versus 15.1%; 95% CI 0.20-0.71; *P*=.003).[15] Although out of the scope of present study, the effect of chronic use of statin on the incidence of CI-AKI in this study cannot be ruled out.

The mean highest serum creatinine for AKI was 193 umol/L (eGFR 36 mL/min/1.73 m^2) versus no AKI -175 umol/L (eGFR 40 mL/min/1.73 m^2). In this study, oral NAC was primarily used. The oral route has been recommended as the cost of oral is more affordable than intravenous NAC, and the efficacy of intravenous NAC to in preventing CI-AKI is inconclusive.[16] In one study, either a high (1200 mg) or low dose of NAC (600 mg) reduced CI-AKI compared to the control group, with the incidence of CI-AKI at a significantly lower rate in the high-dose NAC group.[17] As such, an oral high-dose NAC oral regimen was chosen over the IV route. The incidence of CI-AKI varied by radiological procedure, from 2-3% of CI-AKI patients with stroke undergoing CT to 9-12% in patients with pulmonary embolism undergoing CT angiography.[18,19] Underlying patient factors also affected the CI-AKI incidence with the general 2% incidence in general population increasing to nearly 50% in high-risk patients with comorbidities such as renal impairment and diabetes mellitus.[20] To date, the recommendations for renal failure patients undergoing contrast-enhanced procedure are focused on nonpharmacologic approaches, thus avoiding contrast media, and nephrotoxic medications while general immediate dialysis after contrast administration is not warranted to preserve residual renal function.[21] High-contrast volume is known to increase the risk of developing CI-AKI and the risk increases proportionally to the volume of contrast.[22,23] A threshold volume of contrast, calculated using 5 mL/kg body weight divided by serum creatinine (mg/dL) (maximum 300) was suggested in an effort to minimize CI-AKI in percutaneous coronary intervention. A volume exceeding the threshold predicts AKI requiring dialysis.[24]

Hypotension as an independent risk predictor was found in a few studies.[13,25] Hypotension itself may lead to renal hypoperfusion and ischemic nephropathy, which increases the risk for further contrast-induced kidney injury.[23] Another possible explanation could be that hypotensive patients (SBP<90 mm Hg) tend to be more critically ill and require inotrope support, thus are more vulnerable to kidney insult, thereby raising the incidence of CI-AKI. Many studies have concluded that prior hydration therapy is a predictive factor for CI-AKI.[13,26] Adequate hydration acts to dilute contrast media concentration in blood plasma and tubular cells. The POSEIDON trial showed a significant reduction in CI-AKI incidence, 16.3% versus 6.7%, respectively, in the control and fluid groups.[27] Thus prior hydration therapy and continued post-contrast-enhanced procedure should always be implemented for all high-risk patients as it is the only recommended prevention strategy to date.[4] Nevertheless, fluid administration need to be carefully monitored as overhydration may precipitate pulmonary edema in patients with renal impairment or cardiac congestive failure.[27]

The efficacy and safety of other pharmacological agents are conflicting, with inconsistent findings. Many are no longer considered appropriate as preventive treatment.[28] In our study, use of statins and calcium channel blockers did not shown any significant difference in affecting AKI. There is inadequate evidence to support the withdrawal of nephrotoxic drugs prior to contrast-enhanced procedure in stable elective patients.[29] In our study, 28 patients used biguanides and

no significant difference was found between AKI vs no AKI groups. On the other hand, the term nephrotoxicity in this study was applied to drugs that are commonly found to be associated with nephrotoxicity, namely angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocker (ARBs), aminoglycosides (gentamicin, amikacin), vancomycin, diuretics, calcineurin inhibitors (cyclosporine, tacrolimus), acyclovir and nonsteroidal anti-inflammatory drugs (NSAIDs).[30] Although metformin is not a nephrotoxic drug on its own, special caution should be taken with metformin use in renally impaired patients as metformin is excreted mainly via the kidney. Metformin should be discontinued at the time of contrast media use and resumed 48 hours after the procedure.

A limitation of this study is that there was no differentiation of other confounding factors for development of CI-AKI, which may have flawed the estimation of the actual CI-AKI prevalence. As our study was intended to understand the use of NAC for CI-AKI prevention in the local setting, all patients prescribed NAC for CI-AKI were included in the analysis. This may cause a wide variation in baseline and clinical characteristics in study populations and the confounding variables may cause increased heterogeneity in results. As this study is cross-sectional study, it estimates association with CI-AKI development, but not actual causality. To ensure judicious use of a drug, all patients undergoing a contrast-enhanced procedure should be assessed carefully and stratified according to risk for CI-AKI incidence.

In conclusion, both hypotension and use of high contrast volume significantly increased the odds for the presence of AKI incidence while prior hydration therapy showed protective effects against the development of AKI. The incidence of CI-AKI can be minimized early recognition of underlying risk factors and implementation of precautionary steps including adequate hydration therapy and minimization of contrast volume.

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