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원 저

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Low-dose Intravenous N-acetylcysteine for the Prevention of Contrast-Induced Nephropathy in Emergency Patients Undergoing Computed Tomography

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Purpose: To evaluate the effects of low-dose intravenous N-acetylcysteine on the prevention of contrast-induced nephropathy (CIN) in patients undergoing computed tomography (CT).

Methods: All patients presenting to our emergency department and undergoing CT with intravenous contrast media between August 2014 and April 2016 were retrospectively enrolled. We included hospitalized patients with renal dysfunction [estimated glomerular filtration rate (GFR) between 30 and 89 mL/min/1.73 m^2]. A 600-mg injection of N-acetylcysteine was given to patients once before and once immediately after CT, depending on the preference of physician. The primary outcome was CIN defined as an increase in creatinine level of $\geq$25% or $\geq$0.5 mg/dL from the baseline within 48 to 72 hours after CT. A trained person blindly reviewed all medical records.

Results: Of the 1903 admitted patients, CIN occurred in 9.8% of patients who received 1200 mg intravenous N-acetylcysteine (24/244) and 6.8% of patients who did not (113/1659, p=0.090). In a multivariable regression analysis, N-acetylcystine was not relevant to the prevention of CIN (odds ratio=1.42 [95% CI, 0.90-2.26]). Even in the stratified analysis using the propensity score matching, N-acetylcysteine was irrelevant (GFR 30-59: odds ratio=1.06 [95% CI, 0.43-2.60]; GFR 60-89: odds ratio=1.76 [95% CI, 0.75-4.14]). After adjustment, crystalloids were significantly associated with the reduction in CIN compared with dextrose water (odds ratio=0.60 [95% CI, 0.37-0.97]).

Conclusion: No effect was found when low-dose intravenous N-acetylcysteine was used to prevent CIN. However, there seems to be an association between crystalloids and reduction in CIN.

Key Words: Acute kidney injury, Contrast media, N-acetylcysteine

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Introduction

Contrast-induced nephropathy (CIN) is a decrease in renal function occurring after the administration of radio-contrast media[1,2]. CIN was uncommon in patients with normal renal function, ranging from 0% to 10%[3]. However, the incidence may be as high as 25% in

patients with preexisting renal impairment or certain risk factors, such as diabetes, congestive heart failure, advanced age, and concurrent administration of nephrotoxic drugs[1]. Generally, CIN is known to be transient, and reversely recovered[4]. However, CIN may occasionally lead to a prolonged hospitalization, and increased morbidity or mortality so that active prevention and treatment may be required[1]. Many methods have been studied to reduce or prevent CIN; hydration, administration of N-acetylcysteine, sodium bicarbonate, statins, or ascorbic acid, withdrawal of nephrotoxic drugs, and use of low-osmolar contrast media[2].

Recently, a meta-analysis reported that low-dose N-acetylcysteine with intravenous saline or statins plus N-acetylcysteine with intravenous saline were the most effective method to reduce CIN[5]. However, many studies enrolled either stable outpatients or patients having intra-arterial procedures that used intra-arterial contrast media. Besides, N-acetylcysteine was mostly given to patients via the oral route. Considering the urgent nature of computed tomography (CT) scan in the emergency department (ED), there is a limit to the oral administration of the drug over time.

As a diagnostic tool, the use of contrast-enhanced CT has rapidly increased due to the short shooting time and accuracy of diagnosis in the ED[6]. Thus, there' s also likely to be an increase in CIN and preventive measures may be required more often than in the past. However, a few studies have been carried out by low-dose intravenous N-acetylcysteine in emergency patients undergoing CT with intravenous contrast media.

The aims of this study were to evaluate the effect of low-dose intravenous N-acetylcysteine as a preventive method of contrast-induced nephropathy in hospitalized patients who had undergone a contrast-enhanced CT in the ED and to identify risk factors associated with CIN following CT to support an effective preventive strategy in the ED.

Methods

1. Study design and setting

This was a retrospective study conducted at a 600-beds teaching hospital in South Korea. In recent years, our ED had an average census of 53,000 patient-visits per year. In our ED, the use of preventive measures for CIN was at the discretion of the physician considering the patient' s condition and clinical situations. Among them, intravenous bolus administrations of 600-mg N-acetylcysteine before and immediately after CT scan were the most commonly used. The local institutional review boards approved this study. Informed consent was waived for electrical medical records and computerized provider order entry systems review.

2. Selection of participants

Patients older than 18 years who underwent contrast-enhanced CT of the brain, chest, abdomen or pelvis at our ED from August 2014 to June 2016 were eligible for the study. We primarily enrolled patients who admitted to our hospital to obtain the follow-up creatinine level. Patients with a baseline estimated glomerular filtration rate (GFR) between 30 and 89 mL/min/1.73m^2 were selected for analysis because the preventive measures were likely performed in patients with a moderate risk of contrast-induced nephropathy. We excluded patients who had end-stage renal disease currently undergoing regular hemodialysis or peritoneal dialysis. The following patients were also excluded from the study: patients who did not have a baseline eGFR analysis performed before CT scan; patients who had a baseline eGFR below 30 or above 89 mL/min/1.73m^2; patients who received other preventive measures for CIN, such as sodium bicarbonate, ascorbic acid or statins within 72 hours; patients who did not have a follow-up serum creatinine analysis performed 72 hours after CT scan; patients who received another dose of contrast medium within 72 hours.

3. Data collection and measurement

We retrospectively identified all patients undergoing a contrast-enhanced CT scan at our ED during the research period by assessing the medical records and order entry systems. In a similar way, we collected the following data: age, sex, mean blood pressure at the time to visit our ED, comorbidities (hypertension, DM, congestive heart failure, chronic kidney disease, liver cirrhosis, cerebrovascular accident), and recent use of medicine (nonsteroidal anti-inflammatory drugs, angiotensin receptor blockers, diuretics, and HMG-CoA reductase inhibitors). We also recorded laboratory and clinical information, such as hemoglobin level, serum albumin level, baseline and follow-up creatinine levels, and administrated fluid and contrast media type. Hemoglobin and serum albumin levels were recorded as an initial value which was achieved, since patients had presented to the ED. Baseline renal function was assessed by GFR using the most recent serum creatinine value within 14 days before the CT scan. Fluid type was defined as an initial fluid which was administered to a patient in the ED.

4. Outcome measures

The primary outcome was the incidence of contrast-induced nephropathy (CIN). CIN was defined as an increase ≥0.5 mg/dL or ≥25% above baseline in the serum creatinine level within 48 to 72 hours after CT. We used an initial creatinine value which was achieved in the ED before the CT scan as the baseline. If there was no creatinine value obtained before the CT scan, but there was a creatinine result within 14 days in our medical records, we also used it. The secondary outcome was the all-cause in-hospital mortality. All data collection and outcome measurement was performed by a trained assessor who was blinded to the objectives of the study using a standardized data form through the medical records and order entry systems review.

5. Statistical analysis

We analyzed the compiled data with descriptive statistics. Data are expressed as frequencies and percentages, means and standard deviations, or median and range, as appropriate. Chi-square or Fisher exact tests were used for categorical variables, and t test or Wilcoxon rank sum test for continuous variables.

A multivariate logistic regression analysis was used to evaluate the effect of N-acetylcystine on CIN and to identify the variables that had an independent effect on CIN. All variables with p values 〈0.1 by univariate analysis were considered for the multivariate logistic regression model.

To reduce the influence of patient selection and estimate the association between CIN and N-acetylcysteine, we performed a propensity-score-matched analysis. All collected variables were used in propensity score matching except GFR. To minimize the effect of the inherent renal function on CIN, which was the most important risk factor of CIN7), we stratified the patients by a baseline eGFR: 30-59 and 60-89 mL/min/1.73m^2 corresponding to chronic kidney disease stage 2 and 3, respectively. We performed a 3:1 nearest-neighbor matching with a caliper distance of 0.2 without replacement based on the estimated propensity score of each patient. The standardized difference was used to evaluate the match balance of all variables included in the propensity score matching. An absolute standardized difference of ≤10% was considered appropriate.

All statistical tests were 2-sided and a p value 〈 0.05 was considered statistically significant. The SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for statistical analysis.

Results

1. Characteristics of the patients

Of all patients undergoing the contrast-enhanced CT during the study period, 6624 patients were admitted. There were 2646 patients who met exclusion criteria (Fig. 1). For analysis, we also excluded

2075 patients who did not have a follow-up serum creatinine level in 72 hours after the CT scan, because we could not determine whether CIN occurred.

A total of 1903 patients, 244 patients (12.8%) received low-dose intravenous N-acetylcysteine. Table 1 shows the characteristics of the patients before and after propensity score matching. In an unmatched analysis, there were significant differences in age, some comorbidities, use of medications, serum albumin and creatinine, GFR, and contrast type (Table 1). After stratification into two layers of GFR, patients were matched based on their propensity score, resulting in 79 patients who received N-acetylcysteine and 237 patients who did not in GFR 30-59 group, and 91 patients who received N-acetylcysteine and 273 patients who did not in GFR 60-89 group. There was no significant difference on any of the baseline after matching for propensity score.

2. Main results

Of the 1903 patients, 137 patients (7.2%) had CIN. There was a trend toward a higher incidence of the N-acetylcysteine group (24/244; 9.8%) compared with controls (113/1659; 6.8%) (OR=1.49; 95% CI, 0.94-2.37; p value=0.090), but no difference between two groups after adjustment (OR=1.42; 95% CI, 0.90-2.26; p value=0.132) (Table 2). After adjustment,

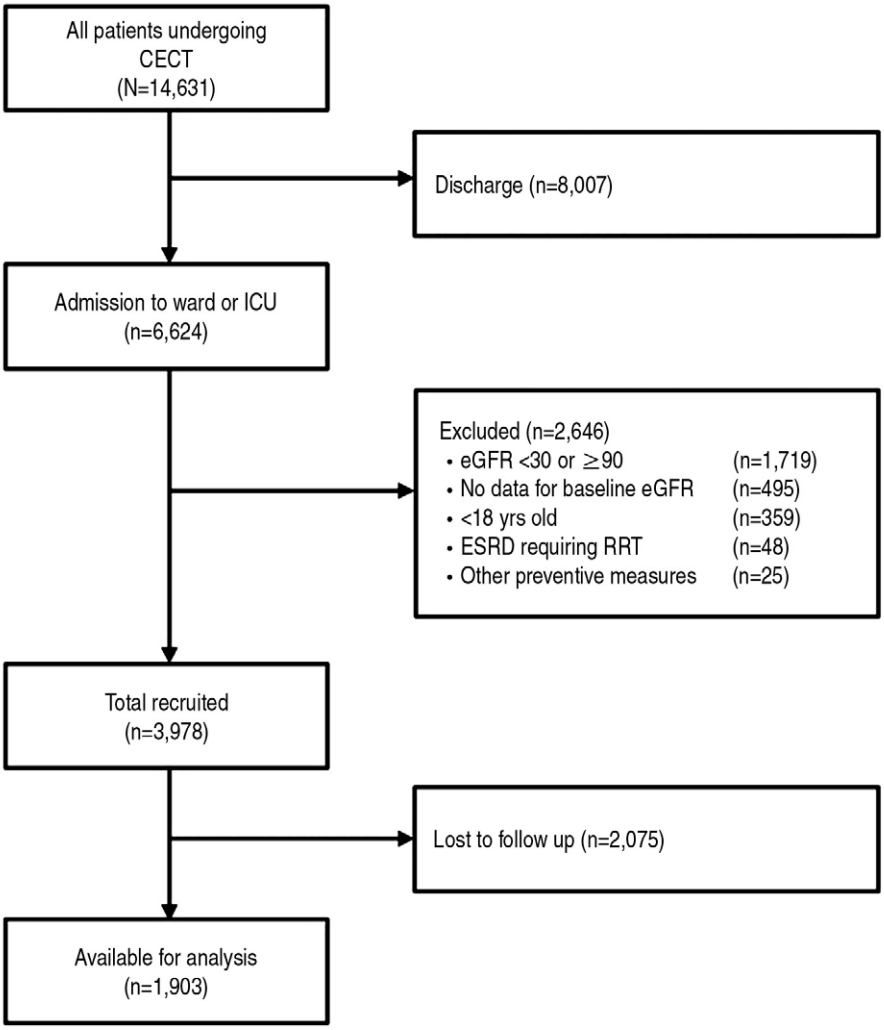

Fig. 1. Flow chart of the study cohort.
CECT: contrast-enhanced computed tomography, eGFR: estimated glomerular filtration rate, ESRD: end stage renal disease, RRT: renal replacement therapy

Table 1. Baseline characteristics before and after propensity score matching*

Characteristics	Before matching (N=1903)				After matching							
					GFR 30-59 (N=316)				GFR 60-89 (N=364)			
	Control (n=1659)	NAC (n=244)	*p* value	SD	Control (n=237)	NAC (n=79)	*p* value	SD	Control (n=273)	NAC (n=91)	*p* value	SD
Male	868 (52.3)	129 (52.9)	.873	1.10	135 (57.0)	43 (54.4)	.694	-5.09	131 (48.0)	44 (48.4)	.952	0.72
Age, y	69 (18-96)	74 (20-99)	<.001	37.68	76 (18-96)	76 (32-98)	.714	-1.49	71 (20-95)	68 (20-99)	.754	1.31
MBP ≥65†	1560 (94.0)	233 (95.5)	.362	-6.56	212 (89.5)	71 (89.9)	.915	-1.38	269 (98.5)	90 (98.9)	1.00	-3.29
Comorbidities												
Hypertension	810 (48.8)	153 (62.7)	<.001	-28.22	150 (63.3)	50 (63.3)	1.00	0	142 (52.0)	49 (53.9)	.762	-3.69
DM	419 (25.3)	100 (41.0)	<.001	-33.88	88 (37.1)	29 (36.7)	.946	0.87	80 (29.3)	28 (30.8)	.791	-3.21
CHF	37 (2.2)	4 (1.6)	.553	4.28	8 (3.4)	2 (2.5)	1.00	5.02	0	0	NA	
CKD	44 (2.7)	17 (7.0)	<.001	-20.29	23 (9.7)	6 (7.6)	.574	7.51	0	0	NA	
Liver cirrhosis	68 (4.1)	5 (2.1)	.120	11.90	12 (5.1)	3 (3.8)	.769	6.13	2 (0.7)	1 (1.1)	1.00	-3.89
CVA	163 (9.8)	39 (16.0)	<.001	-18.42	28 (11.8)	9 (11.4)	.920	1.31	33 (12.1)	14 (15.4)	.417	-9.57
Medication												
NASIDs	104 (6.3)	7 (2.9)	.034	16.34	11 (4.6)	3 (3.8)	1.00	4.18	2 (0.7)	1 (1.1)	1.00	-3.89
ARBs	104 (6.3)	22 (9.0)	.107	-10.36	31 (13.1)	9 (11.4)	.696	5.16	8 (2.9)	3 (3.3)	1.00	-2.13
Diuretics	134 (8.1)	30 (12.3)	.028	-13.98	31 (13.1)	13 (16.5)	.453	-9.54	20 (7.3)	6 (6.6)	.814	2.91
HMG-CoA RI	189 (11.4)	40 (16.4)	.025	-14.50	37 (15.6)	6 (7.6)	.072	25.24	26 (9.5)	8 (8.8)	.835	2.53
Laboratory data†												
Hemoglobin	12.9±2.3	12.6±2.6	.083	-12.22	12.3±2.5	12.3±2.6	.880	0	13.5±2.1	13.3±2.5	.647	-8.66
Albumin	4.0 (1.5-5.7)	3.9 (1.5-5.3)	<.001	-15.34	3.8 (2.3-5.7)	3.8 (1.5-5.3)	.952	0	4.1 (2.1-5.4)	4.1 (1.7-5.2)	.875	0
Creatinine	1.0 (0.6-2.2)	1.2 (0.6-2.2)	<.001	78.45	1.2 (0.7-2.2)	1.2 (0.9-1.7)	.761	0	0.9 (0.6-1.4)	0.9 (0.6-1.4)	.854	0
GFR, mL/min/1.73m²†			<.001	-79.65								
30-59	412 (24.8)	150 (61.5)										
60-89	1247 (75.2)	94 (38.5)										
Contrast type			.032	16.27			1.00	0			.373	-12.02
Low-osmolar	1527 (92.0)	234 (95.9)			222 (93.7)	74 (93.7)			269 (98.5)	88 (96.7)		
Iso-osmolar	132 (8.0)	10 (4.1)			15 (6.3)	5 (6.3)			4 (1.5)	3 (3.3)		
Fluid type			.164	-9.17			.915	1.38			.344	11.9
Crystalloid fluid	1478 (89.1)	210 (86.1)			212 (89.5)	71 (89.8)			239 (87.6)	83 (91.2)		
Dextrose water	181 (10.9)	34 (13.9)			25 (10.6)	8 (10.1)			34 (12.5)	8 (8.8)		

GFR: estimated glomerular filtration rate, NAC: N-acetylcysteine, SD: standardized difference, DM: diabetes mellitus, CHF: congestive heart failure, CKD: chronic kidney disease, CVA: cerebrovascular accident, NSAIDs: non-steroidal anti-inflammatory drugs, ARB: angiotensin receptor blockers, HMG-CoA RI: HMG-CoA reductase inhibitor

* Data are presented as number of patients (%), mean±SD or median (range).

† Initial values at the time of emergency department

there also was no difference of in-hospital mortality between two groups (OR=1.51; 95%CI, 0.89-2.57; p=0.125)

In the propensity-matched cohort, there was no difference in CIN between those who received N-acetylcysteine and those who did not (GFR 30-59: OR=1.06; 95% CI, 0.43-2.60; p=0.908 and GFR 60-89: OR=1.76; 95% CI, 0.75-4.14; p=0.193) (Table 3). In-hospital mortality of the patients who received N-acetylcysteine also was not different from that of patients who did not (GFR 30-59: OR=2.00; 95% CI, 0.7-5.34; p=0.168 and GFR 60-89: OR=2.34; 95% CI, 0.79-6.93; p=0.125).

Among the variables which had p values less than 0.1 in univariate analysis, the independent factor that was associated with CIN was the administration of crystalloid fluid (OR=0.60; 95% CI, 0.37-0.97; p=0.037) (Table 4).

Table 2. Comparisons of contrast-induced nephropathy and in-hospital mortality in patients who received N-acetylcysteine and controls

Group	N	Outcome events (%)	OR (95% CI)	*p* value	Adjusted OR* (95% CI)	*p* value
CIN						
Control	1659	113 (6.8%)	Reference		Reference	
N-acetylcysteine	244	24 (9.8%)	1.49 (0.94, 2.37)	.090	1.42 (0.90, 2.26)	.132
In-hospital mortality						
Control	1659	80 (4.8%)	Reference		Reference	
N-acetylcysteine	244	18 (7.4%)	1.57 (0.93, 2.67)	.094	1.51 (0.89, 2.57)	.125

OR: odds ratio, CIN: contrast-induced nephropathy

* Adjusted by sex, diabetes mellitus, liver cirrhosis, angiotensin receptor blockers, diuretics, hemoglobin, serum creatinine, and fluid type.

Table 3. Contrast-induced nephropathy and in-hospital crude mortality in the propensity score-matched sample with subgroup analysis stratified by initial estimated glomerular filtration rate

Group	GFR 30-59			GFR 60-89		
	Outcome events (%)	Odds ratio (95% CI)	*p* value	Outcome events (%)	Odds ratio (95% CI)	*p* value
CIN						
Control	20 (8.4)	Reference		16 (5.9)	Reference	
N-acetylcysteine	7 (8.9)	1.06 (0.43, 2.60)	.908	9 (9.9)	1.76 (0.75, 4.14)	.193
In-hospital mortality						
Control	11 (4.6)	Reference		8 (2.9)	Reference	
N-acetylcysteine	7 (8.9)	2.00 (0.7, 5.34)	.168	6 (6.6)	2.34 (0.79, 6.93)	.125

GFR: estimated glomerular filtration rate, CIN: contrast induced nephropathy

Table 4. Multivariate logistic regression analysis of factors associated with contrast-induced nephropathy

Factors	OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Female sex	1.35 (0.96, 1.89)	.086	1.09 (0.72, 1.65)	.680
Diabetes mellitus	1.40 (0.98, 2.01)	.068	1.34 (0.90, 1.95)	.128
Liver cirrhosis	1.99 (1.00, 3.97)	.050	1.87 (0.90, 3.88)	.096
History of ARBs use	1.71 (0.97, 3.02)	.064	1.51 (0.83, 2.75)	.178
History of diuretics use	1.79 (1.09, 2.96)	.023	1.51 (0.88, 2.60)	.139
Hemoglobin	1.07 (0.99, 1.15)	.089	1.09 (1.00, 1.18)	.054
Serum creatinine	2.05 (1.08, 3.88)	.028	1.66 (0.78, 3.55)	.190
Crystalloid fluid*	0.54 (0.34, 0.86)	.009	0.60 (0.37, 0.97)	.037

OR: odds ratio, ARB: angiotensin receptor blockers

* Dextrose water is the reference for initially administrated fluid at the emergency department.

Discussion

In this observation study of ED patients at increased CIN risk, we found that intravenous administration of 600 mg N-acetylcysteine before and after CT has no effect on prevention of CIN. However, the use of crystalloid solution as an initial fluid was associated with the reduction of CIN. These findings imply that future trials which are well designed to demonstrate the effect of low-dose intravenous N-acetylcysteine and crystalloid fluid are needed.

CIN is a form of renal impairment or injury that occurs following the intravascular administration of contrast media[8]. CIN is generally defined as an increase ≥0.5 mg/dL or ≥25% from baseline in the serum creatinine level within 48 to 72 hours after contrast administration[9]. The exact pathophysiology of CIN is not clear. Several underlying mechanisms have been suggested. The contrast media cause direct toxic injury to the renal tubules with damage caused by reactive oxygen species[10]. They also cause vasoconstriction mediated by increased adenosine and endothelin and decreased nitric oxide and prostaglandin, resulting in limited blood flow in the outer medulla. In distal tubules, increased interstitial pressure secondary to increased urinary viscosity and contrast-induced diuresis reduces GFR. These mechanisms lead to renal ischemia and subsequently CIN. This phenomenon is exacerbated by contrast media in patients with an impaired renal function such as CKD. Thus, CKD is regarded as one of the most potent risk factors of CIN.

N-acetylcysteine is one of the most frequently investigated regimens for preventing CIN. Although the mechanism by which N-acetylcysteine prevents contrast-induced nephropathy is not well known, in many reports, it minimizes cellular damage by removing oxygen free radicals, and also binds to nitric oxide to make a more stable form with strong vasodilatory effects. Since the landmark study by Tepel et al.[11], which demonstrated efficacy for oral administration of 600-mg N-acetylcysteine twice daily for two days, many similar studies of N-acetylcysteine have been published. However, they have shown conflicting results. Even guidelines have disagreed whether N-acetylcystine prevents CIN and the use of N-acetylcysteine for patients receiving contrast media is recommended[8,12,13].

In a recently published systematic review, oral N-acetylcystine plus intravenous saline compared with intravenous saline had a statistically significant benefit[5]. In patients with receiving low-osmolar contrast media, oral or intravenous N-acetylcysteine plus intravenous saline was also beneficial to CIN. Although the strength of evidence was not high, N-acetylcysteine had an effect on reducing CIN risk. However, there is no benefit of intravenous N-acetylcysteine in that study. Previous reports examining intravenous N-acetylcysteine in patients undergoing contrast-enhanced CT also have provided conflicting results. In a randomized controlled study of patients with at least one CIN risk factor comparing between intravenous bolus N-acetylcysteine 3 g in 500 mL normal saline before CT and 200 mg/hour for up to 24 hours after CT and 500 mL normal saline alone, there was no difference in CIN between two groups[14]. The finding of the study was similar to ours. However, in a randomized controlled study using intravenous bolus of 900-mg N-acetylcysteine before and immediately after CT scan, N-acetylcysteine had a protective effect in CIN[15]. Another prospective study using a single dose (600 mg) of intravenous N-acetylcysteine before CT showed a low incidence of CIN in N-acetylcysteine group[4].

According to the route of administration of N-acetylcysteine, its exact mechanisms for the prevention of CIN are not completely understood. N-acetylcysteine undergoes first pass metabolism in the liver and thus, when given orally, little N-acetylcysteine enters the systemic circulation[16]. It is hypothesized that through first pass metabolism, N-acetylcysteine stimulated the synthesis of glutathione, which exerts a potent antioxidant effect[17]. Another hypothesis is that N-acetylcysteine may also have a direct protective effect on the kidney so that intravenously administrated N-acetylcysteine is more effective[18]. A dose-dependent effect of N-acetylcysteine for the prevention of CIN supports this hypothesis[19]. Although

there is insufficient evidence of intravenous use of N-acetylcysteine for preventing CIN, studies on intravenous N-acetylcysteine have not performed as much as those on oral N-acetylcysteine[5]. Besides, as the use of emergency CT has increased, fast and effective preventive measures for CIN are required. Therefore, more researches of intravenous N-acetylcysteine, one of the preventive measures, are needed to determine the effectiveness for the prevention of CIN.

There is also limited evidence of N-acetylcysteine to patients receiving intravenous contrast media. Most studies focused on patients receiving intra-arterial contrast media, such as percutaneous coronary angiography[5]. Considering the clinical characteristics of emergency patients, it is likely that emergency patients receiving intravenous contrast media have a high incidence of CIN. However, according to the patients that the study enrolled, the development rates of CIN after contrast-enhanced CT significantly vary from study to study, ranging from 2% to 21%[15,20]. Although it is difficult to clearly identify the risk of emergency patients receiving intravenous contrast media, a meta-analysis of patients undergoing CT has shown N-acetylcystine with intravenous saline to be superior to saline alone in reducing the risk of CIN[21]. This meta-analysis included all studies in which N-acetylcysteine was administered orally or intravenously, but there is the possibility intravenous N-acetylcysteine reduces the incidence of CIN in patients receiving intravenous contrast media.

There are some limitations to the study. First, the data were collected retrospectively by the medical record review. Although the electrical medical record was a structured format and primary physicians were asked to fill up with the whole medical information about the patient, self-reporting bias and missed data might be present. Second, other known factors that influence CIN did not be included in the study. For instance, the infused fluid volume was not able to be checked only from medical record review. Unknown risk factors of CIN could also not be included because of the study design. Thus, selection bias might be present in this retrospective study. However, we used a propensity-score-matched analysis to reduce the influence of patient selection. To control the bias and confounding thoroughly, future randomized controlled studies of the comparative effectiveness of low-dose intravenous N-acetylcysteine are needed. Third, more than half of the recruited patients were lost to follow up as they did not have the subsequent results of serum creatinine within 72 hours. We precluded the patients for analysis because we could not evaluate whether CIN occurs. Fourth, we only recruited patients with mild to moderate reduction in GFR between 30 and 89 mL/min/1.73m^2, corresponding to chronic kidney disease stage 2 and 3[22], which limits generalizability to the full spectrum of patients at risk for CIN. In addition, this study was an analysis of CIN that happened at an ED in South Korea, which also limits the external validity of our results. The results may vary in other settings.

Conclusion

In this retrospective cohort study, there was no preventive effect of low-dose intravenous N-acetylcysteine on contrast-induced nephropathy in hospitalized patients who had undergone a contrast-enhanced CT at an ED. There was a limit to the study because the infused fluid volume was unchecked, but the crystalloid fluid was associated with the reduction of CIN. The use of crystalloid fluid in patients with impaired renal function may be strategies for reducing or preventing CIN at the ED.

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