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Therapeutic Benefits of N-Acetylcysteine in the Management of Contrast-Induced Nephropathy

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Abstract

Objective This study aimed to assess the beneficial effects of N-acetylcysteine (NAC) in the treatment of contrast-induced nephropathy (CIN).

Materials and Methods A prospective study was conducted in the department of cardiology of a tertiary health care hospital. A sample of 100 patients who had developed CIN through coronary angioplasty were categorized into two groups: one group treated with intravenous fluids (IVF) monotherapy and the other group treated with the combination of IVF and NAC therapy.

Statistical Analysis The data were analyzed using statistical software SPSS software version 26 and statistical significance was set at $p < 0.05$. Independent *t*-test and paired *t*-test were used to analyze the parameters.

Results The rate of incidence of CIN was found to be 10%. We observed that the IVF + NAC combination therapy significantly decreases the serum creatinine compared to IVF monotherapy ($p = 0.004$). Both therapies show similar treatment outcomes with no significant difference ($p = 0.556$) in the case of estimated glomerular filtration rate (eGFR). Based on creatinine clearance, the results show adding NAC does not impact any additional benefits ($p = 000$). The duration of hospital stay of the NAC group was reduced significantly ($p = 0.000$).

Conclusion At present, we found that the treatment outcomes which we analyzed based on factors such as serum creatinine, eGFR, and creatinine clearance, are too inconsistent to conclude the beneficial effect of NAC in the management of CIN.

Keywords

- contrast-induced nephropathy
- creatinine clearance
- duration of hospital stay
- eGFR
- N-acetylcysteine
- serum creatinine

Introduction

Contrast-induced nephropathy (CIN) is defined as the impairment of kidney function with a 25% increase in serum creatinine from baseline or a 0.5 mg/dL (44 µmol/L) increase in serum creatinine within 48 to 72 hours after intravenous (IV) contrast administration.[1] It is most commonly observed in patients receiving intra-arterial (IA) administration of iodinated contrast media for cardiac procedures, especially those with preexisting kidney diseases. CIN is the third leading cause of hospital-acquired acute kidney injury (AKI). It is a dose-dependent and severe reaction that occurs following an IV or IA contrast media administration.[2] The usual side effects of injecting radiographic contrast media can go from a mild reaction such as itching to life-threatening and serious conditions like anaphylaxis. Hence, it is vital and crucial for health care workers to have a better understanding about the possible adverse effects of contrast-induced reactions along with their management.[3] However, there is no specific treatment for CIN.

The management of patients with contrast-associated AKI (CA-AKI) includes elimination and avoidance of potential

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kidney insults, hemodynamic and electrolyte assessment, and management and appropriate dose adjustment of medications for the reduction in glomerular filtration rate (GFR). Among those patients with severely decreased kidney function, monitoring for uremic signs and symptoms is needed. Since oxidative stress is involved in the development of CIN, antioxidants might help in the prevention and management of CIN. N-acetylcysteine (NAC), an antioxidant and scavenger of free oxygen radicals, might play a vital role in treating patients with CIN. Few studies concluded that the administration of antioxidants like NAC significantly reduces the incidence of AKI. However, NAC has failed to show conclusive evidence of protecting against the development of CIN when used as a monotherapy.[4,5] The European Society of Cardiology (ESC) guidelines regarding updates of CIN treatment suggest that IV hydration pre- and postprocedure is the only effective measure to prevent CIN. Limited studies have revealed the combined effect of NAC and intravenous fluids (IVF) in the management of CIN. Therefore, we conducted the study with the aim of analyzing the beneficial effects of NAC in the treatment of CIN.

Materials and Methods

Study Design

This is a prospective observational study conducted in the department of cardiology in a tertiary care hospital. The study (project no: 18/058) was approved by the Institutional Human Ethics Committee, PSG Institute of Medical Sciences and Research, and was conducted in accordance with the principles set forth in the Helsinki Declaration.

The study participants were enrolled in the study after obtaining informed consent, and they were provided with a detailed explanation about the study, data to be collected, and the benefits and risks associated with the study. The participants included were patients who had undergone coronary angioplasty and developed CIN, with serum creatinine being increased by 0.3 mg/dL or 50% from the baseline in 48 hours. Patients who refused to give consent, patients in which postprocedural serum creatinine was not available, and patients who had undergone daycare angiogram without hospital stay were excluded from our study.

The therapeutic benefits of NAC as a pharmacological management of CIN were analyzed by grouping the study participants based on their treatment received, in which one group of participants received IVF and another group of participants received the combination of IVF and NAC 20% (which indicates the concentration of NAC solution), 600 mg IV. The sample size was calculated using the formula ($n = 2 \times ([a+b]^2 \times \vartheta^2)/(\mu 1 - \mu 2)^2$ as a result of comparing the mean of two groups. Thus, the sample size for each arm was 50 patients and a total of 100 patients were included in our study.

The data on patient's demography, diagnosis, laboratory values, serum creatinine level, management of CIN with dose and duration, date of procedure, and type of contrast were collected. The patient files and hospital information system (HIS) were utilized as a source of data. The study was conducted for a period of 12 months from January 2019 to January 2020.

Statistical Analysis

The analysis was done using Microsoft Excel and SPSS (Statistical Package for the Social Sciences) software version 26, and statistical significance was set at $p < 0.05$. Independent *t*-test was used to assess the beneficial effect of NAC as a treatment of CIN. Paired *t*-test was used to assess the individual effect of both treatment groups, namely IVF and IVF along with NAC.

Results

The incidence of CIN was found to be 10% as 100 of 1,000 patients who had undergone coronary angioplasty. Out of these 100 patients, the majority (73%; $n = 73$) were males and the remaining were females (27%; $n = 27$). Most of the patients were in the age group of 56 to 65 years (43%), which was followed by 66 to 75 years (22%), 46 to 55 years (21%), 76 to 85 years (8%), and 35 to 45 years (6%).

We considered the patients with estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2 as high-risk patients to develop CIN, whereas patients showing eGFR of 45 mL/min/1.73 m^2 or more are considered low-risk patients.[6] As a conclusion, we found that the majority of our study participants were low-risk patients (88%). In our study, one-half of the population (50%; $n = 50$) was administered IVF along with NAC as a pharmacological management of CIN and the remaining half (50%; $n = 50$) was administered IVF alone.

The majority of the participants (91%) received the contrast medium of iohexol (IOCM) when compared to that of iodixanol (LOCM; 9%). Among the study participants, 89% were with the presence of comorbid conditions and the remaining 11% were with no comorbid conditions. Out of these 89% patients with comorbid conditions, 30% were with only diabetes mellitus, followed by 27% with both diabetes mellitus and hypertension, which was followed by 22% with hypertension and 10% with cardiac disease. These baseline characteristics are mentioned in ►**Table 1**.

We found that both the contrast medium iohexol and iodixanol increased the serum creatinine level from baseline to postprocedure on a mean average of 0.42 ± 0.2 and 0.28 ± 0.5, respectively. However, iohexol significantly increased the serum creatinine level, worsening nephropathy, than iodixanol. This finding is shown in ►**Table 2**.

The individual effects of both treatment groups, IVF + NAC combination therapy and IVF monotherapy based on serum creatinine level, were analyzed using a paired *t*-test with a *p*-value less than 0.05 considered significant. The effectiveness of NAC was analyzed in the IVF + NAC combination therapy group against IVF monotherapy group by using independent *t*-test with significance at $p < 0.05$ based on the serum creatinine levels, eGFR, creatinine clearance, and duration of hospital stay. These findings are highlighted in ►**Table 3**.

Serum Creatinine

The serum creatinine levels postprocedure (coronary angioplasty done with contrast medium) and at the time of

Table 1 Baseline characteristics

Parameters	Observation (%)
Gender	
Male	73
Female	27
eGFR value	
Above 45 mL/min/1.73 m^2	88
Below 45 mL/min/1.73 m^2	12
Management of CIN	
IVF	50
IVF along with NAC	50
Contrast medium	
Iodixanol (LOCM)	9
Iohexol (IOCM)	91
Comorbid condition	
With comorbid condition	89
Without comorbid condition	11
Types of comorbid condition	
DM	30
HTN	22
Cardiac disease	10
DM + HTN	27

Abbreviations: CIN, contrast-induced nephropathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; IVF, intravenous fluid; NAC, N-acetylcysteine.

hospital discharge of both treatment groups were analyzed. The postprocedure level was elevated for both treatment groups. Similarly, the serum creatinine level during hospital discharge (after treatment) was reduced in both groups. The effectiveness of the IVF + NAC combination therapy and IVF monotherapy was individually analyzed using paired *t*-test based on the respective serum creatinine levels postprocedure and during discharge. From this result, we observed that both IVF + NAC combination therapy ($p = 0.000$) and IVF monotherapy ($p = 0.000$) significantly reduce the serum creatinine levels posttreatment until discharge. The mean reduction of serum creatinine from postprocedure until discharge for the IVF + NAC combination therapy was 0.34 ± 0.3 and that for IVF monotherapy was 0.174 ± 0.3. We observed that the IVF + NAC combination therapy significantly decreases the serum creatinine compared to IVF monotherapy ($p = 0.004$).

eGFR

The postprocedure level was reduced in both treatment groups compared to baseline. During discharge, the eGFR level of both groups was slightly high. The mean increase of eGFR for the IVF + NAC combination therapy was 9.15 ± 4 and that for IVF monotherapy was 11.11 ± 3. The mean difference of eGFR between these two groups does not show a significant difference, which indicates both the IVF + NAC combination therapy and IVF monotherapy show similar treatment outcome with no much significant difference ($p = 0.556$).

Creatinine Clearance

The postprocedure level was decreased in both treatment groups. The creatinine clearance level, during discharge, was elevated for both groups. The mean increase of creatinine clearance for the IVF + NAC combination therapy was 13.12 ± 7 and that for IVF monotherapy was 21.46 ± 6. We found that IVF monotherapy significantly increases creatinine clearance than IVF + NAC combination therapy ($p = 0.000$). Adding NAC does not impact any additional benefits.

Duration of Hospital Stay

The mean hospital stay of the IVF + NAC combination therapy was 3.90 ± 3 days and that of IVF monotherapy was 5.14 ± 2 days. The duration of hospital stay of the NAC group was reduced significantly ($p = 0.000$).

Discussion

We observed that combining NAC with the known management of CIN, that is, IVF (combination therapy of IVF along with NAC), shows a better improvement in treatment outcome based on the measurement of serum creatinine levels at different intervals than IVF alone. This is in accordance with a meta-analysis study conducted by Feng et al, which compares the effectiveness of NAC monotherapy, ascorbic acid monotherapy, and combination therapy of NAC and ascorbic acid for prevention of CIN. They concluded that there was significant reduction in serum creatinine level after administration of NAC.[7] Some studies have provided evidence for a dose-dependent effect of NAC with more benefits observed when double doses (1,200 mg IV) of NAC were administered to reduce CIN.[8,9] Further, a meta-analysis on NAC for the prevention of CIN indicates that high-dose NAC may decrease the incidence of CIN.[10] Also, although the diagnosis of CIN was primarily based on the change in serum

Table 2 Effect of contrast medium based on serum creatinine level

Contrast medium	Baseline serum creatinine	Postprocedure serum creatinine	Average mean difference between baseline and postprocedure serum creatinine	*p*-value
Iodixanol (LOCM)	0.96 ± 0.2	1.24 ± 0.3	0.28 ± 0.5	0.15[a]
Iohexol (IOCM)	1.05 ± 0.2	1.48 ± 0.1	0.42 ± 0.2	

[a]Statistically significant ($p < 0.05$).
Note: Unit of both baseline and postprocedure serum creatinine is mg/dL.

Table 3 Effect of IVF therapy and IVF along with NAC therapy

Parameters	Mean value		*p* value
	IVF therapy	IVF + NAC therapy	
Based on serum creatinine level			
Postprocedure	1.34 ± 0.2	1.55 ± 0.1	0.005[a]
During discharge	1.16 ± 0.3	1.21 ± 0.3	0.272
Individual effect of IVF between postprocedure and discharge	1.34 ± 0.2 and 1.16 ± 0.3	–	0.000[a]
Individual effect of IVF + NAC between postprocedure and discharge	–	1.55 ± 0.1 and 1.21 ± 0.3	0.000[a]
Difference between postprocedure and discharge	0.174 ± 0.3	0.34 ± 0.3	0.004[a]
Based on eGFR			
Postprocedure	46.52 ± 4	57.63 ± 1	0.000[a]
During discharge	57.63 ± 5	66.78 ± 2	0.015[a]
Difference between postprocedure and discharge	11.11 ± 3	9.15 ± 4	0.556
Based on creatinine clearance level			
Postprocedure	53 ± 14	40 ± 16	0.000[a]
During discharge	64 ± 10	54 ± 12	0.036[a]
Difference between postprocedure and discharge	21.46 ± 6	13.12 ± 7	0.000[a]
Duration of hospital stay			
Duration of hospital stay	3.90 ± 3	5.14 ± 2	0.000[a]

Abbreviations: eGFR, estimated glomerular filtration rate; IVF, intravenous fluid; NAC, N-acetylcysteine.
[a]Statistically significant ($p < 0.05$).
Note: Unit of parameters based on serum creatinine, eGFR and creatinine clearance are mg/dL, mL/min/1.73m2 and mL/min respectively. The unit for duration of hospital stay is days.

creatinine levels, there are speculations that NAC may directly decrease serum creatinine without improving GFR, possibly by increasing the metabolism of creatinine or by increasing tubular secretion. Our study results show a decrease in serum creatinine levels after administration of NAC.[11] In addition, we observed improvement only in the serum creatinine levels with NAC administration. From the pieces of evidence from the above-mentioned studies along with our results, it is clear that further studies directly comparing the effect of various NAC dose regimens on serum creatinine, creatinine clearance, GFR, and renal blood flow are needed.

Conclusion

At present, we found that the incidence of CIN is about 10% and the treatment outcome which we analyzed based on factors such as serum creatinine, eGFR, and creatinine clearance, are too inconsistent to warrant a conclusion on the beneficial effect of NAC in the management of CIN. The limitation of our study is the small sample size. Further research is required to provide additional evidence on the effectiveness of NAC in CIN management.

Ethics Approval

The study was approved by the PSG Institutional Human Ethics Committee. The approval date and number are February 14, 2018 and IHEC # 086, respectively. Due to the retrospective study design, a waiver of the informed consent was obtained.

Declaration

The study was performed in accordance with the Declaration of Helsinki.

Funding

None.

Conflict of Interest

None declared.

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