www.nephropathol.com DOI: 10.15171/jnp.2018.33 J Nephropathol. 2018;7(3):145-150

Journal of Nephropathology

The standard dose versus double dose of N-acetylcysteine to prevent contrast-induced nephropathy; a randomized controlled clinical trial

Rahimeh Eskandarian[1], Maliheh Yarmohamadi[1*], Maryam Zaker-Tavalae[1], Majid Mirmohammadkhani[2], Marjan Biglari[3], Mohammad Reza Tamadon[3], Tahereh Jalali[4]

[1]Department of Interventional Cardiology, Semnan University of Medical Sciences, Semnan, Iran
[2]Social Determinants of Health Research Center, Department of Epidemiology and Biostatistics, Semnan University of Medical Sciences, Semnan, Iran
[3]Department of Internal Medicine, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran
[4] MPH, Community Medicine specialist, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article type:
Original Article

Article history:
Received: 10 January 2018
Accepted: 4 May 2018
Published online: 25 May 2018

Keywords:
Contrast-induced acute kidney injury, Chronic kidney disease, Angiography

ABSTRACT

Background: Contrast-induced acute kidney injury (CI-AKI) is one of the possible complications in angiography, which its prevention is important. N-acetylcysteine is one of the compounds that has recently been more investigated regarding its effect on CI-AKI.

Objectives: The aim of this study was to investigate the effect of standard dose and twice-the-standard of N-acetyl cysteine on prevention of contrast-induced nephropathy.

Patients and Methods: In a clinical trial, 154 individuals who were referred for angiography and had glomerular filtration rate (GFR) ≤60 mL/min, enrolled in and randomly divided into two groups. Group A received the usual dose of N-acetyl cysteine and group B received twice the standard. Blood urea nitrogen (BUN), creatinine, and GFR values were measured and recorded at intervals before, 24, 48 and 72 hours after angiography. Other required laboratory parameters were also measured and recorded.

Results: The results of this study indicated that the effect of double dose in males and females is not different. It also has a reverse effect on renal function in older patients. Its effect did not differ in diabetic patients compared to non-diabetic patients. N-acetyl cysteine in dose of twice the standard has not any effect on renal function in patients with hyperlipidemia, hypertension, myocardial infarction, pulmonary edema as well as smoker patients. In patients with congestive heart failure (CHF), N-acetyl cysteine in dose of twice the standard had a positive effect on renal function compared with those who did not have CHF. An interesting point in our study was the negative effect of N-acetyl cysteine in dose of twice-the-standard on renal function in patients with lower hemoglobin and hematocrit levels.

Conclusions: Our study showed that an increase in the dose of N-acetyl cysteine is not effective in preventing contrast-induced nephropathy and improving renal function. Of course, in some groups, such as those with CHF, a positive effect was detected. Additionally, in some groups including patients with lower hematocrit and hemoglobin, an increase in dose is associated with a negative effect on renal function.

Original Article

Implication for health policy/practice/research/medical education:
In a clinical trial, on 154 individuals who were referred for angiography or angioplasty and have glomerular filtration rate (GFR) ≤ 60 CC/min showed that an increase in the dose of N-acetyl cysteine is not effective in preventing contrast-induced nephropathy and improving renal function.

Please cite this paper as: Eskandarian R, Yarmohamadi M, Zaker-Tavalae M, Mirmohammadkhani M, Biglari M, Tamadon MR, et al. The standard dose versus double dose of N-acetylcysteine to prevent contrast-induced nephropathy; a randomized controlled clinical trial. J Nephropathol. 2018;7(3):145-150. DOI: 10.15171/jnp.2018.33.

*Corresponding author: Maliheh Yarmohammadi, Email: malihehyarmohamadi@yahoo.com

1. Background

Contrast-induced acute kidney injury (CI-AKI) is the third leading cause of acute renal failure in hospitalized patients with a prevalence of 2% in low-risk people and up to 50% in high-risk groups of the population (1-3). CI-AKI is generally defined as an absolute (≥0.5 mg/dL) or relative (≥25%) increase in serum creatinine concentrations compared to the basal values following exposure to a contrast agent (2). The increase in serum creatinine usually peaks 3 days after receiving the contrast agent and then returns to its initial level after 10 days (4). One of the most important applications of contrast agents is in major angiographies, such as coronary artery angiography. N-acetylcysteine is one of the compounds that has recently been more investigated in terms of its effect on CI-AKI. This compound is a strong antioxidant that can largely neutralize contrast-induced renal toxicity by inhibiting contrast-activated oxygen free radicals (4). In addition to inhibiting oxygen free radicals, N-acetylcysteine can establish normal renal hemodynamics through the effects of vasodilation, and by controlling all the above three mechanisms for the development and progression of CI-AKI, N-acetylcysteine is predicted to be a good medication for the prevention and treatment of CI-AKI (1,2,5). This subject was first studied in 2000, and the results obtained were satisfactory, such that N-acetylcysteine was able to reduce the prevalence of CI-AKI significantly, from 21% to 2% in the group receiving this medication compared to the group that simply received hydration treatment (6). Given all the above information, N-acetylcysteine appears to be a medication with potential effects in preventing and treating CI-AKI, however, the results from different studies, including meta-analysis and independent clinical trials, are not in complete agreement with each other on this subject and have yielded contradictory results (4, 5). The results from a meta-analysis of 41 clinical trials with a total sample size of 6379 showed that N-acetylcysteine reduced the risk of CI-AKI significantly in patients who used this medication (7). The results of another study, however, showed that N-acetylcysteine is only beneficial in patients with basal serum creatinine levels less than 1.9 mg/dL or patients who have received more than 140 mL of the contrast agent (8). The results of an extensive retrospective study conducted on 2308 patients receiving contrast agents showed that the prevalence of CI-AKI was 12.7% in both the N-acetylcysteine and control groups, and the two groups were not significantly different regarding serum creatinine, and this finding contradicts the results of other studies (4). In addition to the contradictions cited in various studies regarding the administration of N-acetylcysteine for the prevention and progression of CI-AKI, different guidelines have also expressed conflicting views. For instance, the Kidney Disease Improving Global Outcomes (KDIGO) guideline has recommended the administration of oral N-acetylcysteine in patients at risk for CI-AKI (9). The American Heart Association and the American College of Cardiology have not recommended this medication and considered proper hydration sufficient for the patients (10).

2. Objectives

Given that not many studies have been conducted on the effect of different doses of N-acetylcysteine in preventing CI-AKI, and since there is not much evidence on the prevention of CI-AKI with the administration of high doses of oral N-acetylcysteine, the present study was conducted to determine the effect of standard and twice-the-standard doses of N-acetylcysteine on the prevention of CI-AKI in patients presenting to Kowsar hospital in Semnan in 2016.

3. Patients and Methods

3.1. Study population

This single-blind, randomized, controlled, clinical trial was conducted on 154 patients undergoing coronary artery angiography or angioplasty at the angiography department of Kowsar hospital of Semnan who met the inclusion criteria and consented to take part and who were selected through randomized blocks of 2, 4, 6, 8 and 10. The patients were randomly assigned to either the standard or the twice-the-standard dose list, and they were blinded to the medication they were administered. The two groups were matched as much as possible in terms of age, weight, type of underlying disease, and type and dose of the contrast received. The inclusion criteria were having a glomerular filtration rate (GFR) less than 60 mL/min and age range of 18 and over. The exclusion criteria consisted of being pregnant or breastfeeding, undergoing dialysis, having uncontrolled hypertension (blood pressure ≥160/100 mm Hg), a basal serum creatinine >7 mg/dL, having severe heart valve disease, self-immune diseases, acute or chronic infections, having administered contrast agents over the past 10 days, allergy to contrast agents or N-acetylcysteine, oliguria (a urine volume <400 cc/24 hours), severe heart failure with an ejection fraction of <35% and having received vitamin C supplement in the past week.

The study subjects were divided into group A and B according to the noted randomized allocation method in the following manner;

Group A; intervention group 1 (n=77); receiving oral N-acetylcysteine at the standard dose + saline 9% infusion; receiving a 600-mg dose of oral N-acetylcysteine twice a day for 2 days (1 day before + 1 day after receiving the contrast agent) + saline 9% infusion (100 mL infusion per hour) from 6 hours before to 12 hours after receiving the contrast agent.

Group B; intervention group2 (n=77); receiving oral N-acetylcysteine at the twice-the-standard dose + saline 9% infusion; receiving a 1200-mg dose of oral N-acetylcysteine twice a day for 2 days (1 day before + 1 day after receiving the contrast agent) + saline 9% infusion (100 mL infusion per hour) from 6 hours before to 12 hours after receiving the contrast agent.

Demographic details including age, gender, renal disease pressure, heart failure and type and dose of contrast agent, contrast-induced complications (CI-AKI and hypotension), and laboratory criteria including serum creatinine, blood urea nitrogen (BUN) and GFR before and 24, 48 and 72 hours after receiving the contrast agent, and also the hematocrit levels were recorded.

3.2. Ethical issues

1) The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained; and 3) This study was approved by the Ethics Committee of Semnan University of Medical Sciences (ethical code# IR.SEMUMS.REC.1395.78) and registered in Iranian Registry of clinical Trials (Identifier: IRCT2017052925732N16).

3.3. Statistical analysis

Data were analyzed using statistical tests including the t-test or its non-parametric equivalent (Mann-Whitney's U test) for the quantitative variables, and the chi-square test or Fisher's exact test for the qualitative variables. Wherever possible, a multivariate linear regression model was used for determining whether the underlying variables were matching. The confidence interval was set at 95% and the significance level as $P<0.05$ for all the tests. When the direction of the effect of a variable could not be predicted, the double-range test was used. The results were ultimately expressed as arithmetic mean ± arithmetic standard deviation. A database was created and the input data were presented in the form of tables and figures. Data were analyzed using SPSS 19 and Stata 9.2.

All the data remained confidential, and consents were obtained from all the study subjects, and they were ensured of their right to withdraw from the study at any stage.

4. Results

The present study was conducted on 154 eligible subjects. The patients were randomly assigned into two groups using randomized blocks.

Of all the participating patients, 64 (41.6%) were male and 90 (58.4%) were female. The patients' mean age was 71.45±8.94 years, and the difference between the two groups was not significant ($P=0.865$).

4.1. Analytical results

The analytical results showed no significant differences between the two groups in terms of BUN, creatinine and GFR 24, 48 and 72 hours after the angiography or angioplasty (Mann-Whitney U test).

4.2. The hematocrit effect

Given the cut-off point of 36 for the hematocrit level, the analytical results of comparing the mean BUN, creatinine and GFR before and 24, 48 and 72 hours after angiography in patients with a hematocrit less than and more than 36 showed no significant relationship in group A. Nonetheless, significant differences in mean BUN, creatinine and GFR before and 24, 48 and 72 hours after angiography in the patients with a hematocrite less than and more than 36 (increased BUN and creatinine and reduced GFR; the twice-the-standard dose negatively affected the improvement of the renal function parameters) were observed.

4.3. The effect of chronic kidney disease

Taking into account the effect of chronic kidney disease (CKD), the analytical results of comparing the mean BUN, creatinine and GFR before and 24, 48 and 72 hours after angiography in the patients with and without CKD showed significant differences in BUN and creatinine 24, 48 and 72 hours after angiography. Accordingly, a significant difference in GFR 72 hours after angiography in group A was observed. In group B, however, no significant differences in the mean GFR before and 24, 48 and 72 hours after angiography in the patients with and without CKD was observed. In fact, using a twice-the-standard dose had positive effects on GFR in patients with CKD.

4.4. The effect of congestive heart failure

Study on the impact of congestive heart failure (CHF), the analytical results of comparing the mean BUN, creatinine and GFR before and 24, 48 and 72 hours after angiography in patients with and without CHF showed significant differences in GFR 48 and 72 hours after angiography in group A. In group B, the mean GFR

before and 24, 48 and 72 hours after angiography in patients with and without CHF showed no significant differences. The twice-the-standard dose seems had positive effects on GFR in patients with CHF.

4.5. The effect of the contrast agent

Using a double dose has no effect on renal function parameters depending on the type of administered contrast agent. The results showed no significant differences between groups A and B in mean BUN, creatinine and GFR before and 24, 48 and 72 hours after angiography.

4.6. The impact of the dose of the contrast agent

Using a double dose has no effect on renal function parameters depending on the dose of contrast agent used. The results showed no significant differences between groups A and B in mean BUN, creatinine and GFR before and 24, 48 and 72 hours after angiography.

5. **Discussion**

A total of 154 people were assessed in this study in two groups (n=77 per group) in order to determine the effect of twice-the-standard dose of N-acetylcysteine in preventing CI-AKI. The results showed that using the double dose does not affect the genders differently.

Using the twice-the-standard dose had a positive effect on renal function in people with CKD and CHF compared to those without. An interesting point in this study is that the twice-the-standard dose had a negative impact on renal function in patients with a low hemoglobin and hematocrit, and it can be argued that double-dose should not be administered to such patients.

Studies on the effect of N-acetylcysteine in preventing nephropathy and improving renal function in people receiving contrast agents have yielded contradictory findings, and such results were also observed in the present study.

A clinical trial conducted by Richter et al in the United States showed that of 302 patients assessed (151 who received N-acetylcysteine and 151 who received saline), renal function was significantly worse in the N-acetylcysteine group compared to the saline group (serum creatinine level; 1.415 mg/dL versus 0.95 mg/dL, respectively; $P<0.001$). However, the percentage of those with advanced contrast-induced nephropathy (CIN) was significantly lower in the N-acetylcysteine group compared to the other group (10.2% versus 21.8%, respectively; $P=0.042$) (4). These results resembled our findings in many respects. In our study, the twice-the-standard dose had negative effects on renal function in patients with anemia and in the older patients, however the twice-the-standard dose had positive effects on renal function in patients with CKD and CHF.

In another systematic review and meta-analysis conducted in 2015, the role of N-acetylcysteine in preventing CI-AKI was assessed in patients with diabetes and those with mild renal failure. According to the results of the meta-analysis study, CI-AKI occurred significantly less in N-acetylcysteine group in 20 of the studies (OR=0.76, 95%CI: 0.61-0.93; $P=0.008$), but nine of the studies did not find significant differences between the N-acetylcysteine and the control group (OR=0.87, 95%CI: 0.58-1.3; $P=0.5$). The authors of the meta-analysis concluded that N-acetylcysteine can be administered in CI-AKI prevention. However, because of the contradictory results reported in different studies, providing definite proof of this argument requires further research (11). Our findings are in some ways similar to the above results. In our study, negative effects were observed, especially in those with anemia and in the older patients, but the twice-the-standard dose had a positive effect on renal function in the patients with CKD and CHF. These results are also somewhat contradictory.

In another study in 2013, Loomba et al examined the role of N-acetylcysteine in preventing CI-AKI as reported in different studies. The analysis of the results obtained from different studies showed that the intravenous or oral administration of N-acetylcysteine can be administered in preventing CI-AKI, although no significant relationship was observed between this medication and the need for dialysis or patient mortality. This meta-analysis also showed that using N-acetylcysteine has no relationship with the dose or type of the contrast agent. It seems that the exact role of N-acetylcysteine in preventing CI-AKI is challenging still and need further investigations. Further studies are therefore required in this field, while future meta-analysis can offer more precise explanations of the subject (12).

Our results are very similar to the results of the Loomba et al study. Our study also showed no relationship between N-acetylcysteine administration and the dose and type of the contrast agent.

One review study assessed the biological and pharmacological characteristics of N-acetylcysteine to determine its CI-AKI preventive effects. The results showed that N-acetylcysteine reduces creatinine levels significantly. They suggested that the practical dose

for the CI-AKI -preventive effect of N-acetylcysteine should exceed 600 mg/d (13).

We considered an increase in dose and compared the effect of the double dose with the standard dose. While the double dose was found to have no effect on renal function in many cases. Additionally it had a negative effect on people with low hemoglobin and hematocrit values, which contradicts the hypothesis proposed in the study by Fishbane et al. Nonetheless, increasing the N-acetylcysteine dose to twice-the-standard improved renal function in some groups, including in the patients with CKD and CHF, which somehow confirms the effect of the double dose of the medication in this group of patients.

In a study conducted by Briguori et al in Milan, Italy, the effect of the standard and double doses of N-acetylcysteine were compared in preventing CI-AKI. A total of 224 patients with chronic kidney failure presenting for coronary and peripheral artery angiography were included in this randomized clinical trial. No significant relationship was observed between the dose of the contrast agent and the severity of CI-AKI in two groups when a low dose of the agent was administered. However, a significant relationship was observed when high doses were used. It is possible that, when high doses of contrast agent were administered, the severity of CI-AKI would be significantly higher in the group that received the standard dose of N-acetylcysteine than the group that received the twice-the-standard dose. The authors thus concluded that the twice-the-standard dose of N-acetylcysteine is more effective than the standard dose in preventing CI-AKI (14).

The results of the above study resembled the present findings. In the present study, the patients with CKD and CHF received a twice-the-standard dose of N-acetylcysteine and experienced an improvement in their renal function, which is consistent with the results of the above study. Nevertheless, receiving higher doses was not associated with positive effects in other groups. For example its negative effects were even perceived in this respect in the patients with a low hemoglobin and hematocrit values.

In a meta-analysis study conducted to assess the effect of a maximum dose of N-acetylcysteine in preventing CI-AKI in clinical trials in which the patients who received a single daily dose of more than 1200 mg oral N-acetylcysteine or more than four 600-mg doses per day, while 38.7% of the participants were diabetic. The authors concluded that using a maximum dose of N-acetylcysteine is significantly effective in preventing CI-AKI (15).

Our findings suggest that increasing the dose has no effect on diabetic patients. The positive effects were only observed in patients with CKD and CHF, while in cases with a low hemoglobin and hematocrit, increasing the dose had negative effects, which disagrees with the results of the cited meta-analysis.

Conclusions

The present study showed that increasing the dose of N-acetylcysteine is not effective in preventing CI-AKI or improving renal function in people receiving contrast agents. Nevertheless, positive results were observed in some groups, such as in patients with CKD and CHF, while people with a low hematocrit and hemoglobin experienced adverse renal outcomes when their dose was increased.

Limitations of our study

Given the contradicting results of this and other studies, larger-scale studies are recommended to be conducted on the long-term effects of contrast agents on renal function.

Acknowledgments

This article is part of an MD thesis by Maryam Zaker-Tavalae (# 259), approved by the Research Deputy of Semnan University of Medical Sciences. We would like to thank the Clinical Research Development Unit of Kowsar Educational and Research and Therapeutic Center of Semnan University of Medical Sciences for providing faclities to this work.

Authors' contribution

MY conducted the research and contributed to the conception and design of the research. MRT prepared the primary draft. MZT contributed to the acquisition of data. MM contributed to the analysis of data. RE contributed to the drafting of the manuscript and final approval of the manuscript.

Competing interests

The authors declare that they have no competing interest.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Funding/Support

This study was supported and funded by the Research

Deputy of Semnan University of Medical Sciences (Grant # 331-5).

References

1. Koc F, Ozdemir K, Kaya MG, Dogdu O, Vatankulu MA, Ayhan S, et al. Intravenous N-acetylcysteine plus high-dose hydration versus high-dose hydration and standard hydration for the prevention of contrast-induced nephropathy: CASIS-- a multicenter prospective controlled trial. Int J Cardiol 2012;155(3):418-23. doi: 10.1016/j.ijcard.2010.10.041.
2. Mehran R, Caixeta A. N-acetylcysteine in preventing contrast induced nephropathy. To give, or not to give: that is the question. Rev Esp Cardiol 2010; 63(1): 9-11.
3. Briguori C, Quintavalle C, De Micco F, Condorelli G. Nephrotoxicity of contrast media and protective effects of acetylcysteine. Arch Toxicol 2011;85(3):165-73. doi: 10.1007/s00204-010-0626-5.
4. Richter SK, Crannage AJ. Evaluation of N-acetylcysteine for the prevention of contrast-induced nephropathy. J Community Hosp Intern Med Perspect. 2015;5(3):27297. doi: 10.3402/jchimp.v5.27297.
5. Bartorelli A, Marenzi G. PCR-EAPCI Textbook- contrast agents and renal protection. https://www.pcronline.com/eurointervention/textbook/pcr-textbook/chapter/?chapter_id=76.
6. Tepel M, Van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrastagent- induced reductions in renal function by acetylcysteine. N Engl J Med. 2000;343(3):180-4. doi: 10.1056/NEJM200007203430304.
7. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrastinduced nephropathy. Ann Intern Med. 2008;148(4):284-94. doi: 10.7326/0003-4819-148-4-200802190-00007.
8. Alonso A, Lau J, Jaber BL, Weintraub A, Sarnak MJ. Prevention of radiocontrast nephropathy with N-acetylcysteine in patients with chronic kidney disease: a meta-analysis of randomized, controlled trials. Am J Kidney Dis. 2004; 43(1):1-9. doi: 10.1053/j.ajkd.2003.09.009.
9. Section 4: Contrast-induced AKI. Kidney Int Suppl 2012;2(1):69-88. doi: 10.1038/kisup.2011.34.
10. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124(23):e574-651. doi: 10.1161/CIR.0b013e31823ba622.
11. Kang X, Hu DY, Li CB, Ai ZS, Peng A. N-acetylcysteine for the prevention of contrast-induced nephropathy in patients with pre-existing renal insufficiency or diabetes: a systematic review and meta-analysis. Ren Fail. 2015;37(10):297-303. doi: 10.3109/0886022X.2015.1012985.
12. Loomba RS, Shah PH, Aggarwal S, Arora RR. Role of N-acetylcysteine to prevent contrast-induced nephropathy: a meta-analysis. Am J Ther. 2016;23(1):e172-83. doi: 10.1097/MJT.0b013e31829dbc1c.
13. Fishbane S, Durham JH, Marzo K, Rudnick M. N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. J Am Soc Nephrol. 2004 15: 251-260. doi: 10.1097/01.ASN.0000107562.68920.92.
14. Briguori C, Colombo A, Violante A, Balestrieri P, Manganelli F, Elia PP, et al. Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. Eur Heart J. 2004;25(3):206-11. doi: 10.1016/j.ehj.2003.11.016.
15. Trivedi H, Daram S, Szabo A, Bartorelli AL, Marenzi G. High-dose N-acetylcysteine for the prevention of contrast-induced nephropathy. Am J Med. 2009;122(9):874.e9-15. doi: 10.1016/j.amjmed.2009.01.035.