SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 4.
Issue: 6.
Page N. 218-224
Year: 2020

Original Article www.wjahr.com

THE ADMINISTRATION OF N-ACETYLCYSTEINE AS PREVENTION OF NEPHROPATHY IN HIGH RISK PATIENTS UNDERGOING CORONARY ANGIOGRAPHY IN TERTIARY CARE HOSPITAL, KARACHI, PAKISTAN

[1]Dr. Syed Meerab Javed, [2]Dr. Afifa Saulat and [3*]Dr. Anwar Nabeel Jafri

[1]MBBS, FCPS Internal Medicine Aga Khan University Hospital, Karachi, Pakistan.
[2]MBBS, FCPS Internal Medicine Aga Khan University Hospital, Karachi, Pakistan.
[3]MBBS, FCPS Internal Medicine Aga Khan University Hospital, Karachi, Pakistan.

Received date: 06 October 2020 **Revised date:** 26 October 2020 **Accepted date:** 16 November 2020

***Corresponding author: Dr. Anwar Nabeel Jafri**

MBBS, FCPS Internal Medicine Aga Khan University Hospital, Karachi, Pakistan.

ABSTRACT

Introduction: Contrast induced nephropathy is reported to be the third most common cause of in hospital acute kidney injury. There are enormous impacts of the development of this complication in terms of hospital stay, morbidity, mortality and long term dialysis dependence. Since there are no appropriate treatments to this complication much of the focus has been on prevention. N-acetylcysteine is one of the most common drugs used in this perspective; however, there are a number of studies with conflicting results regarding the efficacy of this compound. Hence the need to evaluate the significance of this compound in prevention of contrast induced nephropathy in our population. **Objective**:To determine the frequency of contrast induced nephropathy in patients undergoing coronary angiography and intervention receiving N-acetylcystein as a prophylaxis at Aga Khan University Hospital. **Study design:** Cross sectional study. **Settings:** Department of Medicine, Aga Khan University Hospital. **Materisls and Methods:** Patients admitted in coronary care unit, Aga Khan university Hospital, receiving N-acetylcysteine as a prophylaxis for contrast induced nephropathy before coronary angiography and intervention were included in this study provided they meet the inclusion criteria. Serum creatinine were noted at the baseline and then at 48 hours post contrast exposure. An increase of 0.5 mg/dl above the baseline creatinine was labeled as contrast induced nephropathy. Comorbid conditions including diabetes and chronic kidney disease were noted, so were the age of the patient. **Results:** The frequency of contrast induced nephropathy in patients receiving N-acetylcysteine as a prophylaxis for coronary angiography and intervention was found to be 19.6%. The frequency was observed to increase with increase in age of the patients, mean serum creatinine of all patients on presentation was 1.557 (+/- 0.5539) mg/dl. All of these patients received N-acetylcysteine as a prophylaxis for contrast induced nephropathy and the mean serum creatinine 48 hours post exposure to contrast was found to be 1.632 (1.2001) mg/dl. **Conclusion:** Prophylactic administration of N-acetylcysteine for the prevention of contrast induced nephropathy fail to show a benefit in terms of prevention of contrast induced nephropathy, since, the frequency observed in this study was significantly higher to the incidence of contrast induced nephropathy reported in the earlier studies.

KEYWORDS: Contrast induced nephropathy, N-acetylcysteine, contrast media, diabetes mellitus, chronic kidney disease.

INTRODUCTION

The administration of radio-contrast media can lead to a usually reversible form of acute kidney injury that begins soon after the contrast is administered.[1] Contrast induced nephropathy is associated with a greater risk of in hospital morbidity, mortality, prolonged hospitalization, increased health care cost and potentially irreversible reduction in kidney function.

Patients with diabetes and chronic kidney disease are at a greater risk of acquiring contrast induced nephropathy. It has been keyed out as a third leading cause of hospital acquired acute kidney injury.[2],[3],[4] In addition, other

risk factors predisposing to the development of contrast induced nephropathy include administration of the high volume of contrast, use of high osmolality agents, age> 75 years, reduced intravascular volume, hypotension, Intra-Aortic balloon Pump insertion & left ventricular dysfunction.[5]

There has been increasing attempts at preventing this complication in patients undergoing contrast studies. Preventive strategies include limiting the quantity of contrast material used during the procedure, use of low or iso-osomolality agents and intravenous volume expansion with saline infusions, use of bicarbonate solutions and use of pharmacological agents like N-acetylcystein.

N-acetylcystein is a thiol compound with antioxidant and vasodilator characteristics. It has been proposed to prevent contrast induced nephropathy. N-acetylcystein is being commonly used in patients undergoing contrast studies in hospitals and especially in patients undergoing coronary angiography and intervention. There is heterogeneity and conflicting results in the available clinical trials and meta-analyses examining the effectiveness of N-acetylcystein in the prevention of contrast induced nephropathy. Even so, due to its low cost and low risk its use is recommended in patients with renal dysfunction undergoing contrast studies.[6] A randomized controlled trial done to evaluate the efficacy of N-acetylcystein in the prevention of contrast induced nephropathy in patients undergoing coronary angioplasty showed an incidence of 8% with high dose N-acetylcystein (IV bolus 1200 mg before intervention and1200mg PO BID for 48 hours after intervention)with an overall incidence of 19%. Other dosing schedules used include 600 mg IV prior to intervention and 600 mg PO bid after 48 hours.

In Pakistan, no study has been done previously to assess the efficacy of N-acetylcystein in patients undergoing coronary angiography and intervention. Although, a few studies conducted earlier only looked at the incidence of contrast induced nephropathy in patients undergoing coronary angiography and intervention, they did not take into consideration the role of N-acetylcystein in the prevention of contrast induced nephropathy in particular. The overall frequency of contrast induced nephropathy in these local studies was found to be 8-10% and it was seen that the risk increased with diabetes and chronic kidney disease.[7]

This study evaluates the effectiveness of N-acetylcystein in terms of frequency of prevention of contrast induced nephropathy in patients undergoing coronary angiography and intervention receiving N-acetylcystein as a prophylaxis so that future strategies can be made to reconsider the usefulness of this compound.

MATERIALS AND METHODS

Study design: Cross sectional study
Settings: Department of Medicine, Aga Khan University Hospital
Sample size: assuming a frequency of 10% of contrast induced nephropathy in patients receiving N-acetylcystein as a prophylaxis, a confidence level of 95%, 6% margin of error our sample size is 96 patients.

Sampling technique: Non probability purposive sampling.

Sample Selection
Inclusion Criteria
1. Adult patients aged ≥ 18 yrs
2. All patients receiving N-acetylcystein will be included in the study**.**

Exclusion Criteria
1. Dialysis dependent patients
2. Patients undergoing Coronary artery Bypass Surgery after angiography
3. Patients with known allergy to N-acetylcystein

DATA COLLECTION

Patients undergoing coronary angiography and intervention at AKU "Cardiac Catheterization Lab" receiving N-acetylcystein as a prophylaxis were included provided they met the inclusion criteria. Serum Creatinine concentration is measured in our authentic hospital laboratory. Informed consent was taken from the patients or their attendants (in case patients were not able to give the consent themselves due to medical illness). A specially designed proforma were filled out for each patient consenting to be included in the study. Serum creatinine levels were recorded at presentation and then on day 2 post procedure.

DATA ANALYSIS

SPSS – 17 was used for data analysis. Quantitative variable like age, serum creatinine and amount of contrast were presented as mean with standard deviation. Qualitative variables were sex, presence or absence of comorbid like diabetes mellitus, hypertension & chronic kidney disease. Frequency of qualitative variable was presented. Outcome variable would be occurrence of contrast induced nephropathy and taken as qualitative variable. Stratification was done with respect to age, gender, history of diabetes mellitus & chronic kidney disease to count for confounding interactions.

RESULTS

Demographics
Since December 2016 to May 2017 we enrolled 97 patients in our study. There were 67 male and 30 female patients. The mean age of patients enrolled was 61.51 (+/- 11.93) years. Age and gender distribution is shown in following

Figures

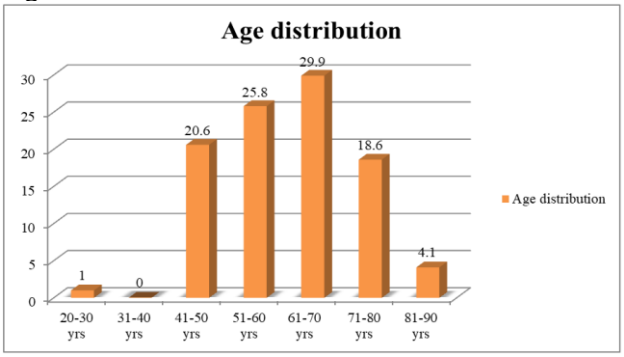


Figure: Age distribution of patients enrolled in study.

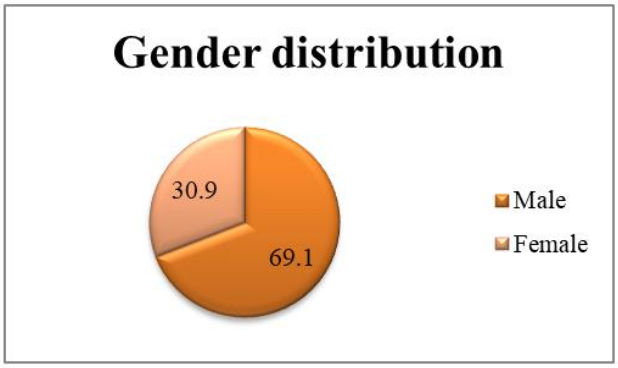


Figure: Gender distribution of patients enrolled in study.

Frequency of diabetes and chronic kidney disease in study population

Patients enrolled were specifically questioned for the presence of diabetes and chronic kidney disease since these are considered to be the main risk factors for the development of contrast induced nephropathy. Total no. of diabetic patients was 60 out of a total number of 97. Of these there were 10 patients who had diabetes of less than 5 years duration, 24 patients with duration of 5-10 years and 26 patients were diabetic for more than 10 years. Patients with chronic kidney disease were 16 out of 97 patients in total. Out of these 2 had chronic kidney disease of less than 1 year, 5 had chronic kidney disease for 2 years, 6 patients had this for 3 years, 1 suffered for 4 years and only 2 patients had chronic kidney disease for 5 years.

The following figures display the same frequencies.

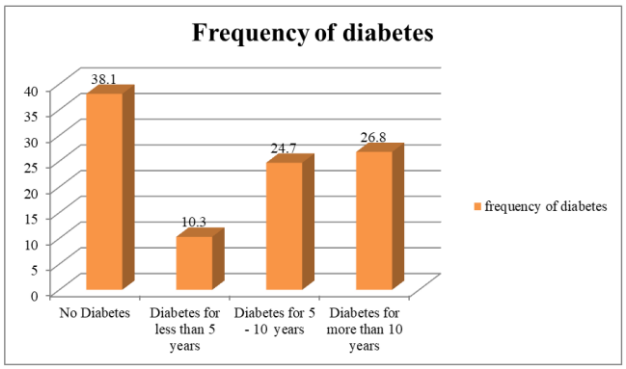


Figure: Frequency of diabetes in study population.

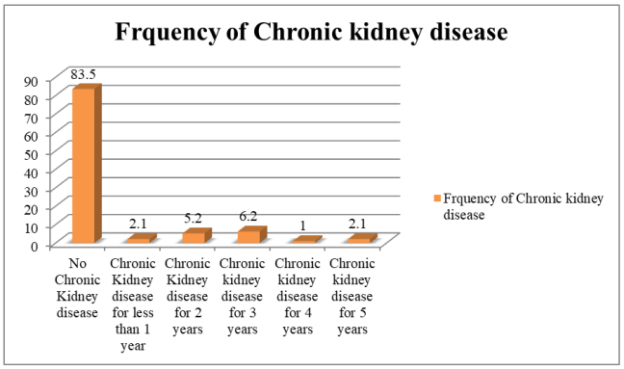


Figure: Frequency of chronic kidney disease in study population.

Serum Creatinine on presentation and at 48 hours post contrast exposure

The mean serum creatinine of all patients on presentation was 1.557 (+/- 0.5539) mg/dl. All of these patients received N-acetylcysteine as a prophylaxis for contrast induced nephropathy and the mean serum creatinine 48 hours post exposure to contrast was found to be 1.632 (1.2001) mg/dl.

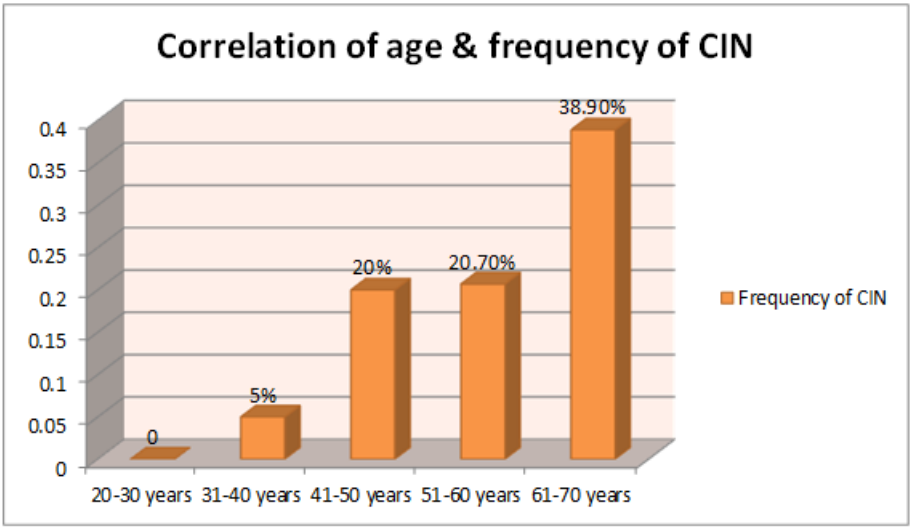
	Number of patients	Minimum	Maximum	Mean
Serum Creatinine on presentation	97	0.4	5.2	1.557
Serum creatinine at 48 hours	97	0.6	8.6	1.632

Frequency of contrast induced nephropathy

Of the study population all of the patients underwent contrast exposure during coronary angiography and intervention and received N-acetylcysteine as a prophylaxis for contrast induced nephropathy. We found that out of 97 patients 19 (19.6%) patients suffered contrast induced nephropathy according to the definition of increase in serum creatinine of 0.5 mg/dl at 48 hours post exposure. The mean age of the affected patients was 60.89 (+/- 11.445) years. Of these 19 patients 13 (68.42%) patients were diabetic, 7 (36.84%) patients had chronic kidney disease and 5(26.31%) patients had both diabetes and chronic kidney disease.

Diabetes		Chronic Kidney disease						Total
		None	For less than 1 years	For 2 years	For 3 years	For 4 years	For 5 years	
No diabetes	CIN	30	0	0	0	1	0	31
	n	4	1	0	1	0	0	6
	y	34	1	0	1	1	0	37
	Total	10	0	0	0	0	0	10
Less than 5 years	CIN		0	0	0	0	0	
	n	10	0	0	0	0	0	10
	y	2	0	1	0	0	1	4
	Total	19	1	2	1	0	1	24
5-10 years	CIN	12	0	3	2	0	0	17
	n	6	0	0	2	0	1	9
	y	18	0	3	4	0	1	26
	Total							
More than 10 years	CIN							
	n							
	y							
	Total							

The mean age of the affected patients was 60.89 (+/- 11.445) years. An increasing trend was observed in frequency of contrast induced nephropathy with the increase in the age of the patient and it was highest in the age group of 61-70 years. This trend is depicted in figure.



DISCUSSION

The potential of N-acetylcysteine in prevention of contrast induced nephropathy has been a topic of great interest, with a number of clinical trials with conflicting results on the efficacy of this compound. Since currently there is no definitive treatment for this important angiography related complications much of the focus has remained on strategies for prevention of contrast induced nephropathy. N-acetylcysteine being a cost effective regimen and relatively free of side effects have been a choice of various interventionists despite its disputed role. This study attempted to identify the significance of this regimen in our population undergoing coronary angiography and intervention. The study attempted to provide a frequency of contrast induced nephropathy in patients receiving N-acetylcysteine undergoing contrast exposure during coronary angiography and intervention so that the results can be compared in light of the available data on this topic in our population and internationally as well. The overall incidence of contrast induced nephropathy ranges from 2% in low risk populations to 50% in high risk populations, including patients with diabetes mellitus, chronic renal insufficiency, advanced age, congestive heart failure and co-administration of other nephrotoxic drugs. The medical and socio-economic consequences of contrast induced nephropathy are thus hazardous, making its prevention of prime importance. A wide variety of strategies have been studied for the prevention but with frustrating results. Apart from peri-procedural saline hydration and use of low osmolarity or iso-osmolar contrast agents the studies on other strategies-including diuretics, vasodilators, anti-oxidants- have been reported to be neutral or even hazardous with conflicting results.

N-acetylcysteine is an anti-oxidant that potentially removes a wide variety of oxygen derived free radicals. It is assumed to be capable of preventing contrast induced nephropathy both by improving renal hemodynamics and by diminishing direct oxidative tissue damage.[8]

Webb *et al.* conducted a large randomized controlled trial to assess the efficacy of N-acetylcysteine in prevention of contrast induced nephropathy in patients undergoing contrast exposure during coronary angiography and intervention.[9] They administered intravenous N-acetylcysteine 500 mg immediately before procedure and concluded that it didn't provided any benefit over placebo in terms of prevention of contrast induced nephropathy.

Pannu *et al.* performed a systematic review and meta-analysis of 15 randomized studies assessing the efficacy of N-acetlycysteine in prevention of contrast induced nephropathy.[10] A total of 1776 patients participated in these studies. They concluded that N-acetylcysteine may reduce the incidence of acute increase in serum creatinine after contrast exposure but this finding was of borderline statistical significance and there were large discrepancies between the trials.

Zagler *et al*. performed another meta-analysis of 13 trials including a total of 1892 patients receiving N-acetylcysteine as a prophylaxis before cardiac catheterization.[11] They concluded that N-acetylcysteine administration before angiography in patients with impaired renal function in an attempt to prevent contrast induced nephropathy can't be recommended as a clinical practice and that further large randomized trials are required since their meta-analysis was inconclusive.

Another recent Turkish trial by Hakan Buyukhatipoglu *et al.* studied 60 patients undergoing coronary intervention and concluded that N-acetylcysteine failed to protect against contrast induced nephropathy. They also claim that their study was the first one to assess clinically the total oxidant capacity and the total anti-oxidant capacity and they found that N-acetylcysteine also didn't affect any oxidant parameters.[12]

Patients with diabetes are at high risk of developing contrast induced nephropathy irrespective of their baseline serum creatinine. Keeping this in view Coyle et al. performed a randomized open label study to assess N-acetylcysteine in prevention of contrast induced nephropathy in diabetics. They randomized 137 patients to receive hydration alone or N-acetylcysteine plus hydration and found that N-acetylcysteine provides no additional benefit over hydration alone in diabetic patients undergoing contrast exposure during coronary angiography.[13]

Carbonell et al. reported that pre-procedural treatment with N-acetylcysteine effectively reduced the risk of contrast induced nephropathy in high risk patients receiving contrast during the coronary angiography and intervention. They enrolled 81 patients with chronic kidney disease (baseline serum creatinine $\geq$ 1.4) and randomized them to receive either N-acetylcysteine 600 mg bid or a placebo. They found that the overall incidence of contrast induced nephropathy was 14.8% with only 5.1% in the N-acetylcysteine group and 23.8% in the placebo group. Hence they concluded that N-acetylcysteine was significantly effective in prevention of contrast induced nephropathy in high risk patients. Carbonell identified two strong points in his study. First, it was a randomized placebo controlled trial in high risk patients undergoing coronary angiography and contrast exposure. Despite the small number of patients in this study, the homogenous and restricted inclusion criteria of patients with baseline renal insufficiency allowed the investigators to appropriately investigate the effects of N-acetylcysteine and placebo on a continuous variable such as serum creatinine increment after coronary angiography. Second, the dose of N-acetylcysteine used was high in comparison to studies done earlier. Carbonell used 600 mg twice daily two days before and two days after the procedure, i.e. a total of 2400 mg, which they proposed to be optimal dosage keeping in view the bioavailability of N-acetylcysteine which is only 20%. In contrast to Carbonell, Webb didn't find any protective effect of N-acetylcysteine. Since the doses used were single low dose without aggressive hydration protocol the results of his study have been biased.

CASIS trial- a multicentre prospective controlled trial-enrolled 220 patients with base line renal insufficiency with a serum creatinine of $\geq$ 1.1 or a creatinine clearance of $\leq$ 60 ml/hr to assess Intravenous N-acetylcysteine plus high-dose hydration versus high-dose hydration and standard hydration for the prevention of contrast-induced nephropathy.[14] They randomized 80 patients to receive intravenous N-acetylcysteine and high dose hydration, 80 patients were randomized to receive high dose hydration only and 60 patients received standard hydration. IV N-acetylcysteine was given as IV bolus of 600 mg of NAC twice daily before and on the day of the coronary procedure (total = 2.4 g). High dose hydration was given as IV 0.9% saline 1 mL/kg/h before, on and after the day of the coronary procedure. Patients in control group received standard hydration protocol as IV dose of 0.9% saline 1 mL/kg/h for 12 hours before and 12 hours after the coronary procedure. They concluded that the results of their study suggested that N-acetylcysteine plus high-dose hydration was superior to high-dose hydration alone as well as standard hydration for the protection of renal functions in patients with mild to moderate renal dysfunction who are undergoing coronary angiography and coronary intervention. Furthermore high-dose hydration without N-acetylcysteine was not better than standard hydration alone. This study is another example of studies in favor of N-acetylcysteine prophylaxis.

In a local study carried out by Dr Aadil Soofi to determine the frequency of contrast induced nephropathy in patients undergoing high dose non-ionic contrast exposure (more than 100 ml of Iopromide) vs. low dose (less than 100 ml of Iopromide) contrast exposure in coronary angiography and intervention, the frequency was 11% in high dose group and 14% in low dose group. This study however didn't specifically looked at the role

of N-acetylcysteine in the prevention of contrast induced nephropathy but it is stated over here since it's a local study and it provides us with an estimation of frequency of contrast induced nephropathy in our own population. A similar study carried out by Uddin *et al*. at Aga Khan University Hospital Karachi, also provides us with the frequency of contrast induced nephropathy in high risk patients undergoing coronary angiography and intervention. They found that the overall frequency of contrast induced nephropathy was 9.65%. The frequency of contrast induced nephropathy was more in patients with high risk co-morbidities. For e.g. patients with pre-existing renal insufficiency suffered more with a frequency of 42.9% (baseline serum creatinine $\geq$ 4 mg/dl). Those with diabetes had a frequency of 11.9%. Again this study didn't specifically looked at N-acetylcysteine as a prophylactic agent but it provides us with significant knowledge regarding the frequency of contrast induced nephropathy in our own population and also characterizes important aspects in terms of co-morbidities affecting the outcome.

If we compare our study in the light of above local and international literature we can easily figure out that the overall incidence of contrast induced nephropathy was 19.6%, which is significantly high in comparison to frequencies presented in earlier studies in our local literature. If N-acetylcysteine were to be of any significance the frequency should have been markedly lower than that observed in previous studies. In our study 13.4% patients with diabetes suffered contrast induced nephropathy where as Uddin et al. reported a frequency of only 11.9% in their study. However this study showed a frequency of contrast induced nephropathy of 7.2% in patients with pre-existing renal insufficiency which is significantly lower than that reported previously in our local literature (Uddin et al. reported it to be 42.9%). From the above findings we can still infer that N-acetylcysteine might be of some benefit in those with pre-existing renal insufficiency. However further studies are required to prove or disprove this fact since there are a few limitations to our study such as:This is not a randomized controlled trial, only admitted patients were selected, other measures preventing contrast induced nephropathy such as saline hydration, sodium bicarbonate infusion and use of non ionic contrast dye were not taken in to account, comorbid conditions apart from diabetes and chronic kidney disease such as congestive cardiac failure, hypertension, left ventricular dysfunction and others which can affect the incidence of contrast induced nephropathy were not addressed, volume and type of contrast agent used were not noted and final outcome of patients suffering contrast induced nephropathy was not followed such as recovery or the development of dialysis dependence.

CONCLUSION

In conclusion, we find that the frequency of contrast induced nephropathy in patients receiving N-acetylcysteine as a prophylaxis of contrast induced nephropathy for coronary angiography and intervention was 19.6%, which is significantly higher in comparison to frequencies of contrast induced nephropathy reported in our local literature earlier. Hence N-acetylcysteine fails to reduce the frequency of contrast induced nephropathy, however, there is some benefit observed in patients with pre-existing renal insufficiency. Further randomizes studies are needed to prove or disprove the usefulness of this compound.

REFERENCES

1. Weisbord SD, Palevsky PM. Radiocontrast-induced acute renal failure. J Intensive Care Med, 2005; 20(2): 63-75.
2. Carbonell N, Sanjuan R, Blasco M, Jorda A, Miguel A. N-acetylcysteine: short-term clinical benefits after coronary angiography in high-risk renal patients. Rev Esp Cardiol, 2010; 63(1): 12-9.
3. Amini M, Salarifar M, Amirbaigloo A, Masoudkabir F, Esfahani F. N-acetylcysteine does not prevent contrast-induced nephropathy after cardiac catheterization in patients with diabetes mellitus and chronic kidney disease: a randomized clinical trial. Trials, 2009; 10: 45.
4. Uddin MA, Rabbani MA, Jafary FH, Bhatti MA, Islam M. Contrast nephropathy in high-risk patients undergoing coronary angiography and intervention. J Coll Physicians Surg Pak, 2005; 15(12): 791-4.
5. Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, et al. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. N Engl J Med, 2006; 354(26): 2773-82.
6. Rezkalla SH. Contrast nephropathy. Clin Med Res, 2003; 1(4): 301-4.
7. Soofi MA. Frequency of acute renal failure after cardiac catheterization and percutaneous intervention. Pak J Med Sci, 2006; 22(4): 446-50.
8. 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.
9. Webb JG, Pate GE, Humphries KH, Buller CE, Shalansky S, Al Shamari A, et al. A randomized controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect. Am Heart J, 2004; 148(3): 422-9.
10. Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. Kidney Int, 2004; 65(4): 1366-74.
11. Zagler A, Azadpour M, Mercado C, Hennekens CH. N-acetylcysteine and contrast-induced nephropathy: a meta-analysis of 13 randomized trials. Am Heart J, 2006; 151(1): 140-5.
12. Buyukhatipoglu H, Sezen Y, Yildiz A, Bas M, Kirhan I, Ulas T, et al. N-acetylcysteine fails to prevent renal dysfunction and oxidative stress after noniodine contrast media administration during percutaneous coronary interventions. Pol Arch Med Wewn, 2010; 120(10): 383-9.

13. Coyle LC, Rodriguez A, Jeschke RE, Simon-Lee A, Abbott KC, Taylor AJ. Acetylcysteine In Diabetes (AID): a randomized study of acetylcysteine for the prevention of contrast nephropathy in diabetics. Am Heart J, 2006; 151(5): 9-12.
14. 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, 2010; 22.