EFFECT OF N-ACETYLCYSTEINE ON DERANGED RENAL FUNCTIONS IN PATIENT RECEIVING NON IONIC RADIO CONTRAST

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ABSTRACT

Objective: To determine the effect of N-Acetylcysteine (NAC) on deranged renal functions in patients receiving non-ionic contrast.

Study Design: Quasi- experimental study.

Place and Duration of Study: The study was conducted in the Department of Radiology, DHQ Hospital Rawalpindi, RMC and Allied hospitals from August 2011 to January 2012.

Methodology: Eighty consecutive patients with deranged renal function tests (RFTs) (creatinine level ≥ 1.3 mg/dl and ≤ 3 mg/dl and urea level > 50 mg/dl) were included in this study. These patients were advised to take at-least eight sachets of NAC to talling to 1,600 mg (one sachets is 200 mg) within two days with good hydration (6 to 8 glasses of water) prior to Contrast Enhanced Computer Tomographic (CECT) scan. After completion of NAC recommended dose, the RFTs are repeated to confirm the controlled range. The patients are allowed for CECT, if the serum urea level ≤ 50 mg/dl (reference range 0-50mg/dl) and serum creatinine level ≤ 1.3 mg/dl (reference range 0.2-1.2 mg/dl).

Results: The mean age of the patient is 53.98±15.4 years. The use of NAC extensively improves the serum urea level of 73 out of 80 patients (91.3%) with a significance of 0.0001 to a normal level (<50 mg/dl). Similarly, serum creatinine level of 71 out of 80 patients (88.8%) with a significance of 0.0001 has an improved from reference range (≤1. 2 mg/dl).

Conclusion: Use of NAC resulted in improved serum urea and creatinine levels in the majority of patients.

Keywords: Deranged RFTs, N- Acetylcysteine, Non ionic radio contrast.

INTRODUCTION

Contrast Induced Nephropathy (CIN) is the third most common cause of acute renal failure in hospitalized patients[1-4]. It is a serious complication resulting in increased health care costs, prolonged hospital stay, dialysis and death[1-3]. Contrast-induced nephropathy is defined as" increase in serum creatinine concentration of ≥0.5 mg/dl (44 _mol/l) or 25% above baseline within 2 days/48 hours after contrast administration."[5]

N-Acetylcysteine (NAC) is an important active agent. It rapidly acts against CIN by causing vasodilatation, improvement of blood flow in the renal medulla, and antioxidant properties[2,6]. The drug's pharmacokinetics are remarkable for almost complete first pass metabolism after oral administration, resulting in no free drug reaching the circulation[7].

The NAC's sulfhydry[1] group may inhibit angiotensin-converting enzyme which reduces production of the vasoconstrictor angiotensin II. The vasoconstriction in CIN may be affecting the kidney's medullary circulation. NAC's recently demonstrated action is in reducing urinary albumin excretion[7].

On the basis of the initial study by Tepel et al[5] NAC is used as a part of the protocol to prevent CIN in many hospitals. Other attributes of NAC that make it an attractive option include its easy administration, with better tolerability and inexpensive solution lead it as a suitable option[8]. It is very important to detect changes of renal function after administration of contrast medium (CM) and to develop strategies for prevention[7].

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In the present study, we demonstrate the efficacy of NAC in patients with impairment of renal function, which were referred to our institution for CECT scan.

METHODOLOGY

This was a quasi-experimental study conducted at the Radiology Department of DHQ Hospital during August 2011 to Jan 2012. This study included 80 non-probability consecutive subjects of both genders with an age range of 10-80 years with deranged RFTs through non-probability consecutive sampling. Before enrollment informed consent was taken from the patient including an explanation of the pros and cons of the procedure. For CECT all subjects received low Osmolar Non-Ionic Radio Contrast.

The inclusion criteria were, patients with deranged RFTs (serum creatinine level ≥ 1.2 mg/dl & ≤ 3 mg/dl and serum urea level was >50 mg/dl) and receiving low osmolar non ionic radio contrast. The patients who have been advised fluid restrictions by their physicians were not included in this study. A reference range of serum urea and serum creatinine is 10-50 mg/dl and 0.2-1.0 mg /dl respectively.

All subjects with deranged RFTs (as per inclusion criteria) were given NAC as described in table 1.

After 48 hours of recommended dosing, RFTs of these subjects were repeated for verification of controlled rage that is serum urea level ≤ 50 mg/dl (reference range 0 mg/dl – 50 mg/dl) and serum creatinine level ≤ 1.2 mg/dl (reference range 0.2 mg/dl - 1.2 mg/dl). The subjects were brought for (CECT) scan, if they satisfied above ranges of urea and creatinine level.

Data Analysis

Data was entered and analyzed using SPSS version 17. Descriptive statistics were used to describe the results. McNamara's test was used to evaluate the change in the values of urea and creatinine levels.

RESULTS

This study was based on 80 patients of both genders. The ages of patients ranged from 18 to 80 years with mean age of 53.69± 15.75 years.

Table 2 shows the value of urea and creatinine level before and after NAC dose. There wasa noteworthy difference in pre and post NAC values of urea and creatinine regardless of age.

Table 3 shows details of the results in relation to the effect on serum urea / creatinine level after NAC on all subjects with the results after McNamara's test was applied. It described the significance of the study. This test is useful in pre and post treatment of NAC. The results of RFTs showed noteworthy improvement. The serum urea level was improved to reference range from 91.3% (73 Patients) and creatinine level was improved to normal range in 88.8% (71 patients). Similarly, the patients who did not show any improvement in the results of RFTs table 3.

DISCUSSION

Administration of contrast media for the diagnostic procedure is the third most common cause of CIN in hospitalized patients[2]. CIN is a common clinical problem. CIN occurring in this setting is associated with increased morbidity and mortality rates, leads to prolonged hospital stay, and greatly increased health care costs. For the prevention of CIN, NAC along with hydration were found to be more effective as compared to placebo[5].

NAC in clinical medicine is primarily used as mucolytic agent. NAC has a number of properties including anti-oxidant functions and mediation of renal vasodilatation that suggests it could help to prevent CIN[7, 13]. Moreover, NAC is inexpensive, easy to administer and has good tolerability. There are some positive results of randomized studies on NAC which has gained favor in clinical practice to use it as a preventive therapy in high-risk group i-e patients with

preexisting renal insufficiency[8]. NAC is also helpful in reducing urinary albumin excretion[7].

Table-1: Protocol for preventing CIN in patients undergoing CECT scan.

Dosing
Before the procedure, administer a 1,600 mg (800 mg twice daily) one sachets is of 200 mg oral dose for 48 hours – Two sachets per dose.
Hydration
Advised for good hydration (6 to 8 glasses of water/ day for 48 hours) before the procedure.

Table-2: Impact of NAC over different factors.

Variables	Patients (n=80) mean ± SD
Age	53.59 ± 15.75
Initial serum urea	73.74 ± 29.20
Initial serum creatine	1.69 ± 0.31
Serum urea after NAC	37.40 ± 12.67
Serum creatinine after NAC	0.99 ± 0.28

Our study proved that the prophylactic administration of NAC is helpful for the patients with deranged RFTs. As the result showed improvement in urea level of 91.3% (73 patients) with significance 0.0001 and creatinine level of 88.8% (71 patients) with a significance of 0.027 to a reference range.

Several randomized control studies and multiple meta-analysis were also performed on NAC during last five years, which gave contradictory / different results. These studies showed that the NAC along with hydration significantly decrease the threat of CIN in high-risk patients[5]. The study of Tepel et al[9] first reported that NAC plus hydration is more effective than hydration alone in preventing CIN[9]. Our results are comparable to this study.

The study by Briguoriet al[9] also emphasized the significance of acetylcysteine dosage. This study showed that the oral administration of a double dose of NAC (1200 mg after every 12 hours) was more effective than standard dose of NAC (600 mg after every 12 hours). The study of Baker e t al[6] showed that the high-dose of NAC was also effective when given intravenously.

Marenzi et al[10] randomly assigned 354 patients of myocardial infarction undergoing coronary angiography with primary angioplasty[10]. In one of three groups: NAC (600 mg) intravenous bolus was given to 116 patients prior to primary angioplasty and four doses of NAC (600 mg) orally every 12 hours after angioplasty. Similarly 119 patients received double dose of NAC (1200 mg) intravenous bolus and 1200 mg orally in every 12 hours after angioplasty and 119 patients were given placebo. They selected both the oral and intravenous route for the administration of NAC. The risk of CIN was reduced by 54.5% in the standard-dose NAC group and by 75.8% in the high-dose NAC group. This effect was particularly impressive and it was not found in previous studies.

Oldemeyer et al[2] randomly assigned 96 patients undergoing elective coronary angiography. One group was double-blind, and another one was placebo-controlled group. They received 1500 mg NAC or placebo, starting the evening before angiography and given twice daily for 48 hours. In their study CIN occurred in 8.2% (4/49) of patients taking NAC and 6.4% (3/47) of patients taking placebo. Their study indicates that NAC does not reduce the risk of CIN, inspite of giving high dose. It was probably because of the truly blind NAC therapy.

Shyu et al[11] randomly assigned 121 patients with a serum creatinine level 2.8 mg/dl or a creatinine clearance <40 ml/min but >8 ml/min to the NAC or placebo. They received 800 mg NAC for two days before the procedure. CIN occurred in 3.3% (2/60) NAC treated patients and 24.6% (15/61) placebo-treated patients (p<.001). This study showed that with the use of NAC serum creatinine level decreased as compared to the patients, who received placebo (p< .01).

Table-3: Results of serum urea and creatinine after NAC.

Status after dose	Serum urea	Serum creatinine	*p*-value
	n (%)	n (%)	
Improved to controlled range	73 (91.3)	71 (88.8%)	0.0001
Not improved	7 (8.8%)	9(11.3%)	0.0001
Total	80(100%)	80(100%)	

Allaqaband et al[12] randomly assigned 85 patients with a serum creatinine level 2.1 mg/dl or a creatinine clearance <60 ml/min in placebo, 0.1µg/kg per minute fenoldopam, or NAC. CIN occurred in 15.3% with placebo, 15.7% with fenoldopam, and 17.7% with NAC (*p*<. 92).

The meta-analysis by Birck et al[14] showed that, the administration of NAC significantly reduced the risk of CIN in patients with preexisting renal insufficiency compared with hydration alone.

The results of these trials, when considered with the results of the present study, indicated that the prophylactic use of NAC is helpful to normalize the deranged RFTs of the patients undergoing CECT scan. Three trials showed clear evidence of benefit, however two trials found no evidence of benefit.

The degree of baseline serum creatinine level in our study was ≥1.3 mg/dl to ≤3 mg/dl and was similar to the other studies ranged from 1.6 mg/dl to 2.8 mg/dl[2,9-12]. Similar to our studies, good hydration (at least 6 to 8 glass water) was recommended to the patients prior to the CECT scan[2,9,11].

The NAC dose was 2400 mg in two of the studies[9,12]. The dose of NAC in the study by Oldemeyer et al was 6000 mg and does not reduce the risk of CIN inspite of giving high dose[2].In the study of Marenzi et al[10] they compared standard dose of NAC 600 mg intravenous bolus and 1200 mg orally after intervention with double dose 1200 mg intravenous bolus and 2400 mg/dl orally after intervention. Their study showed that administration of high dose was more effective than standard doses. The dose of NAC in the study by Shyuet al, only 1600 mg, demonstrated the greatest benefit with NAC[11]. In our study dose of NAC was also 1600 mg/dl, which showed the similar results.

NAC was given as 2 doses before and 2 doses after angiography in three of the studies[9,11-12]. However, Oldemeyer et al[2] gave 1500 mg NAC, starting the evening before angiography and given every 12 hours for 4 doses. In our study NAC was given as four doses before the CECT scan.

Most of the studies showed that the effect of NAC was dose dependent. The high dose of NAC along with hydration was more helpful to reduce the risk of CIN. Oldemeyer et al[2] used the largest dose, however no benefit was observed. It was probably because of brief period of 24 hours to 48 hours monitoring for changes in renal function after angiography, and the ability to truly blind NAC therapy. They did observe gastrointestinal side effects with NAC in 16% of patients[2].

The limitations of our study included relatively small sample size (n=80) as compared to other studies[2,9-12] in these studies they randomly assigned more patients. Moreover, we only evaluated renal function at 48 hours prior to the CECT scan, however the evaluation of post CECT renal function test was not performed due to follow up issue with patients. However, another three published NAC trials[2,9-11] follow-up of all the patients was done up to 48 hours after the procedure. The results of the above discussed three studies out of five[2,9-12] significantly had

same results. However the difference in remaining could be due to difference in protocol and study design. The larger sample size could produce more clear role of NAC in the prevention of CIN in patients undergoing CECT.

Other drugs are also used to prevent contrast induced nephropathy including calcium antagonists, theophylline, ascorbic acid, fenoldopam, and periprocedural hemofiltration. The protective effect of fenoldopam may increase blood flow of the renal medulla in patients at risk of CIN[5]. However other drugs showed evidence of heterogeneity of results[9].

CONCLUSION

NAC is used as a preventive measure in high risk patients, those undergoing CECT/other procedures. After the use of NAC along with hydration serum urea creatinine level was improved, this enabled patients for important investigations leading to effective diagnosis and management. Similarly, NAC is easily administered; a low cost drug which can help to prevent this fatal complication. Our suggestion regarding future studies is to evaluate other drugs for prevention of CIN as limited studies have been done.

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