

Evaluating the Efficacy of Single Daily Dose of 1200mg of N-Acetyl-Cysteine in Preventing Contrast Agent-Associated Nephrotoxicity

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Abstract

Background: Renal toxicity of contrast media remains an up-to-date challenge. N-Acetylcysteine is an antioxidant agent which efficacy has been proved in various models of experimental renal ischemia and therefore proposed in the prevention of renal failure due to intravenous iodine contrast media.

Effects of prophylactic administration of N-acetylcysteine to prevent contrast agent-associated nephrotoxicity (CAN) are controversial.

Aims: This study was designed to evaluate the efficacy of 1200mg once daily administration of NAC on the day before and on the day of imaging on preventing CAN.

Methods: Seventy patients with renal insufficiency (creatinine level ≥ 1.3 mg/dl), referred to our institution for abdominal or chest CT scanning, were randomly assigned to receive either only 0.9 saline 1 hour before contrast dye administration (control group) or 0.9% saline intravenously 1 hour before CT scan and NAC 1200mg single daily dose one the day before imaging and at contrast media injection day (case group). Both groups were comparable in demographics, disease states, drug regimens, and risk factors for developing contrast-agent-induced nephrotoxicity. There were no significant differences between the two groups in type of CT scan, or volume and concentration of contrast used. All patients received 140ml IOHEXOL (300mg I/ml) before CT scanning.

CAN was defined as a rise in serum creatinine of 0.5 mg/dl within 48-72 hours after dye injection.

Results: Seventy patients (35 in each group) completed the study. In the case group, the median of Scr concentrations before receiving the contrast agent, 24, 48 and 72 hours afterward were 1.43, 1.41, 1.51, 1.45 mg/dl respectively. The median of Scr concentrations in the control group before administration of the contrast agent, 24, 48, 72 hours afterward were 1.31, 1.41, 1.48, and 1.61 mg/dl, respectively. The median change in Scr concentrations was greater in the control group than in the case group ($p = 0.04$).

Increase of at least 25% of the creatinine concentration from baseline 72h after the procedure occurred in 12/35 patients (34%) in the control group and 5/35 patients (14.2%) in case group.

The percentage of patients developing acute renal failure was significantly greater in the control group than in the case group ($P = 0.021$).

Conclusion: The use of prophylactic oral NAC combined with IV hydration, significantly reduced the rise in Scr levels within 48-72h after the administration of contrast media.

INTRODUCTION

Administration of Radiographic Contrast Agents (RCA) often results in an acute reduction in renal function. The reduction can cause substantial morbidity and mortality

during hospitalization and can lead to chronic end-stage renal disease. RCA reduce renal function by altering renal hemodynamic and by exerting direct toxic effects on tubular epithelial cells. There is accumulating evidence that reactive

oxygen species have a role in the renal damage caused by contrast agents. The main risk factors for RCA-induced reductions in renal function are preexisting renal dysfunction, particularly which caused by diabetic nephropathy and reduced effective arterial volume (1).

In patients with renal insufficiency, hydration has been reported to ameliorate RCA-Induced reductions in renal function but the administration of drugs such as calcium antagonists, theophylline, dopamine and atrial natriuretic peptide dose not prevent the reduction (2).

N-Acetyl Cysteine (NAC) is a compound that has several attributes making it a potentially useful agent to prevent CIN, besides its antioxidant properties there are reports of its ability to block the expression of vascular-cell adhesion molecule 1. Owing to these properties, in addition to its safety and low cost, NAC may be effective for prevention of CIN (3).

Clinical studies evaluating the efficacy of NAC, have yielded mixed results.

In this study we assessed the effect of oral administration of NAC in prophylaxis of RCI renal insufficiency.

METHODS

We prospectively studied 70 patients with a serum creatinine concentration above 1.2mg/dl (or creatinine clearance of less than 50mL/min). Only patients known to have a history of renal failure and with stable Scr were included, repeated measurements during the 3 days before administration of the contrast agent revealed only minor changes in Scr concentrations (± 0.03 mg/dl). Patients with acute renal failure were excluded. The causes of renal insufficiency were diabetic nephropathy(25), nephrosclerosis(5), glomeronephritis(5), tubulointerstitial nephritis (6) and unknown (19).

All the patients underwent elective abdominal or chest computed tomography (CT scanning) with a Non- Ionic low-Osmolality RCA.

The study protocol was approved by the local ethics committee and all patients gave written informed consent.

STUDY PROTOCOL

The patients were randomly assigned to receive either the NAC and intravenous saline (NAC group) or only saline (control group).

NAC was given orally at a dose of 1200mg once daily on the day before and the day of administration of the contrast agent.

1000 ml saline (0.9%) was given intravenously at a rate of 1ml/kg/hr of body weight 1 hour before contrast dye administration. 140ml IOHEXOL was used as RCA for all patients. The infusion contained 647 mg of iohexol per milliliter and the 300mg iodine content was per milliliter.

None of the patient received theophylline, dopamine, mannitol or furosemide during the study. Serum creatinine was measured repeatedly 3 days before administration of the contrast agent and the day of administration, 24, 48, 72 hrs after RCA administration.

An acute contrast agent induced reduction in renal function was defined as an increase in the Scr concentration of at least 25% of baseline 48-72hrs after administration of the RCA.

RESULTS

The clinical and biochemical characteristics of the patients are shown in table 1. The mean weights of the patients were similar (control group, 71 \pm 8kg, NAC group 74 \pm 8kg) suggesting a similar fluid balance.

Figure 1

Table 1: The clinical and biochemical characteristics of the patients

Characteristic	NAC=35	Control=35	P value
Weight(kg)	74 \pm 8	71 \pm 8	0.5
Age (year)	59.76 \pm 1.99	55.89 \pm 12.92	0.3
Sex (M/F)	17/13	19/11	0.08
Blood Pressure (mmHg)	135/75 \pm 18/11	142/75 \pm 21/13	0.1
Baseline Scr (mg/dl)	1.43 \pm 0.50	1.31 \pm 0.15	0.15
Scr at 24h	1.41 \pm 0.2	1.41 \pm 0.18	0.21
Scr at 48h	1.51 \pm 0.01	1.48 \pm 0.05	0.19
Scr at 72h	1.45 \pm 0.59	1.61 \pm 0.01	0.09

In the control group, serum creatinine concentration increased from 1.31 \pm 0.15 to 1.61 \pm 0.01, 72hrs after administration of the contrast agent (p=0.01). In the NAC group the mean Scr concentration increased from 1.43 \pm 0.5 to 1.45 \pm 0.59 mg/dl (p=0.4) 72hrs after administration of the contrast agent.

An acute contrast agent induced reduction in renal function was defined as an increase in the Scr concentration of at least 25%, 48-72 hours after administration of contrast agent that occurred in 16 patients of the 70 patients (22.8%). 5 of the 35 patients in NAC group (14.2%) and 12 of the 35 patients in control group (34%).

10 of the 16 patients with an acute contrast agent-Induced

reduction in renal function had diabetes mellitus.

In the acetyl cysteine group 12 patients (34%) had base line Scr concentration above 1.5mg/dl as did 6 patients (17%) in the control group. Among these patients with elevated baseline Scr 3 of the 12 patients in the acetyl cysteine group and 4 of 6 patients in control group had an acute contrast agent-induced reduction in renal function.

Among those patients who had contrast agent induced renal insufficiency, 6 of 12 patients in control group showed <25% increase in base line Scr in 48hr. In the case group 2 of 6 patients in 24hr and another cases, 72 hr after contrast administration contrast agent indeed nephropathy was observed.

DISCUSSION

RCA reduce renal function by altering renal hemodynamics and by exerting direct toxic effects on tubular epithelial cells. There is accumulating evidence that reactive oxygen species have a role in the renal damage caused by contrast agents (4).

RCA increased lipid peroxidation and superoxide dismutase in kidney tissue. A scavenger of reactive oxygen species can preserve renal function (5).

Tepel et al reported the ability of NAC in preventing of CIN but in several studies after Tepel's study, there were conflicting results in the ability of NAC to prevent CIN (1).

The finding of this study is that prophylactic oral administration of the acetyl cysteine reduced the incidence of acute contrast agent induced reductions in renal function.

The incidence of acute contrast-agent-induced reduction in renal function varies from zero to 90 percent depending on the presence of risk factors including chronic renal insufficiency, diabetes mellitus and a higher volume of contrast agent administered (6,7).

There were several studies to assess the ability of NAC to prevent CIN (Contrast Induced nephropathy) but there were conflicting results in these studies (8,9).

In Sandhu C et al study they found, there is no benefit to the prophylactic administration of N-acetylcysteine in patients undergoing peripheral angiography using current contrast media (10).

Briguori C et al study showed Nephrotoxicity of iso-

osmolality and low-osmolality contrast agents was similar when a prophylactic strategy of hydration plus NAC was utilized (11).

There were many confusing points in such studies such as dose of NAC, different base line Scr, different variation of patients with comorbidity, different hydration protocols and different risk factors.

One of the conflicting points is that, CIN may occur beyond 48hr after contrast administration but in studies increasing in scr only detected in 48 hrs and it may be the cause of such conflicting results as in our study. Among those patients who had contrast agent induced renal insufficiency, 6 of 12 patients in control group showed <25% increase in base line Scr in 48hr. In the case group 1 of 4 patients in 24hr and another cases, 72 hr after contrast administration contrast agent indeed nephropathy was observed.

If we detected CIN only in 48 hr 5 patients in control group and 3 patients in case group could be missed.

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