Reno-Protective Effect of N-Acetyl Cysteine in Patients with Impaired Renal Function Undergoing Coronary Angiography and Interventions

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Abstract

Background: The increasingly frequent use of contrast enhanced imaging for diagnosis or interventions in patients with CAD has generated concern about avoidance of contrast induced nephropathy (CIN). Reactive oxygen species have been shown to cause CIN.

Objectives: Angiographic contrasts worsen the renal function in patients with renal failure. We studied the reno-protective action of the antioxidant N-Acetyl cysteine (NAC) in patients undergoing coronary procedures.

Methods: Retrospective analysis of 51 patients with elevated serum creatinine levels (≥1.5 mg%) was done, 24 of whom received NAC prior to the procedure (NAC group) and 27 who did not (Non NAC group). NAC was administered in a dose of 400 mg twice daily for four doses starting on the day prior to the procedure. Both groups of patients were hydrated with 0.45% saline at 1 ml/kg/hr for 12 hours prior to and 12 hours following the procedure. Both groups were comparable with regard to age, sex, coronary risk profile, myocardial infarction history, left ventricular function and the drugs received. Serum urea and creatinine were measured on the day prior to and the day following the angiographic procedure.

Results: Nine out of 51 patients developed more than 0.5 mg% rise in serum creatinine level; 1 in the NAC group and 8 in the non NAC group (p<0.05), 24 hours after injection of the contrast medium. In the NAC group mean serum creatinine level decreased from 1.94 ± 0.56 to 1.67 ± 0.56 and blood urea from 47.58 ± 20 to 41.58 ± 15.1. In the non NAC group serum creatinine increased from 1.75 ± 0.31 to 1.98 ± 0.56 and blood urea from 44.96 ± 15.5 to 52.85 ± 20.1 (p<0.05). This corresponds to an increase in creatinine clearance from 30 ml/min to 35.92 ml/min in the NAC group and a decrease from 34.42 ml/min to 29.87 ml/min in the non NAC group. There was no significant difference in the levels of sodium and potassium before and after the procedure in both the groups.

Conclusion: We conclude that prophylactic administration of N-Acetyl Cysteine along with hydration diminishes the incidence of deterioration of renal function induced by contrast agents in patients with renal insufficiency during coronary angiographic procedures.

INTRODUCTION

Contrast induced nephropathy (CIN) is a known risk of coronary interventions. Patients with renal disease frequently also have significant Coronary Artery Disease (CAD) and are referred for Percutaneous Coronary Intervention (PCI). Therefore, the renal complications of PCI have an increasingly important role, as a cause of peri-procedural morbidity and mortality.

The likelihood of occurrence of contrast nephropathy is closely related to preexisting renal dysfunction and the dose of contrast agent used. CIN frequently complicates primary PCI for Acute Myocardial Infarction (AMI) even in patients with normal renal function. A Risk Score for prediction of occurrence of CIN after PCI has been developed. The best approach to contrast nephropathy is prevention. However prevention or mitigation of renal failure after the administration of contrast agent has been difficult to obtain. Hydration has been reported to ameliorate contrast nephropathy in Chronic Renal Failure (CRF) patients. Administration of drugs such as calcium antagonists, theophylline, dopamine and Atrial Natriuretic Peptide (ANP) does not prevent CIN.

Contrast agents reduce renal function by altering renal haemodynamics and exerting direct toxic effects...
on tubular epithelial cells. Renal free radical production increases after administration of contrast agents.\textsuperscript{12} Although pathogenesis of CIN is not fully understood, reactive oxygen species seem to have a role.\textsuperscript{12-14} In animal studies superoxide dismutase, a scavenger of reactive O\textsuperscript{2} species prevents renal damage by contrast agents.\textsuperscript{12}

Acetylcysteine has been shown to have a beneficial effect in preventing renal complications after contrast CT scan.\textsuperscript{13,14} A recent meta-analysis also favoured the use of N Acetyl Cysteine for the prevention of CIN after angiographic procedures.\textsuperscript{21}

The aim of the study was to assess the efficacy of N Acetyl cysteine (NAC) in the prevention of deterioration of renal function in patients with renal failure undergoing coronary angiographic procedures.

\textbf{Material and Methods}

Retrospective analysis of 51 patients with elevated serum creatinine level (\textgeq 1.5 mg\%\textsuperscript{2}) prior to coronary angiography was done. 27 patients did not receive NAC. 24 patients who underwent coronary angiography after the protocol for administration of NAC in patients of renal failure was established in our hospital, received NAC.

NAC was administrated in a dose of 400mg twice daily for 4 doses, starting on the day prior to coronary angiography. Both groups of patients received hydration with 0.45\\% saline at 1ml / kg / hr. for 12 hours prior to and 12 hrs following the coronary procedure.

Blood parameters including blood urea, serum creatinine, creatinine clearance and electrolytes, were measured on the day prior and the day following the coronary procedure (Table 1).

\begin{table}[h]
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\begin{tabular}{|c|c|c|}
\hline
Characteristics & NAC & Control \\
& n=24 & n=27 \\
\hline
Age (mean) & 62.8 ± 10.7 & 66 ± 7.3 \\
Gender (M/F) & 23/1 & 25/2 \\
Serum creatinine & 1.94 ± 0.56 & 1.75 ± 0.32 \\
Blood urea & 47.5 ± 20 & 45 ± 15.5 \\
Creatinine clearance & 39ml/min & 41ml/min \\
Hypertension & 19(76\%) & 20(74\%) \\
Diabetes mellitus & 16(64\%) & 15(59\%) \\
Dyslipidemia & 14(56\%) & 6(22\%) \\
H/O MI & 9(36\%) & 12(44\%) \\
Angiography/angioplasty & 17/7 & 18/9 \\
Dose of contrast agent & 110 ± 3ml & 112 ± 5ml \\
\hline
\end{tabular}
\caption{Clinical and biochemical characteristics of the study patients}
\end{table}

\textbf{Angiographic Procedures}

Coronary angiography with /without angioplasty was performed according to standard clinical practice, using femoral approach. All patients received Iohexol (Omnipaque) as contrast agent. Dose of contrast agent was decided by each patient’s cardiologist. Patients who underwent PTCA received 10,000 units heparin during the procedure, followed by additional boluses if required.

\textbf{Statistical analysis}

Data are expressed as mean value \textpm SD. Differences in serum creatinine concentrations between the groups were analyzed by the student T test.

Differences in serum creatinine concentrations and blood urea before and after angiography /PTCA within the same group were analyzed by the paired T test.

\textbf{Results}

Patient population; A total of 51 patients were included in the study. Their clinical and biochemical characteristics are shown in Table 1. The number of patients with diabetes hypertension and dyslipidemia was similar in both the groups. The volume of contrast agent used in both the groups was similar. The number of coronary angiograms or angioplasty procedures in both the groups was also similar. The two groups were also similar with regard to the drugs they received.

Changes in renal function; 9 patients out of the 51 developed more than 0.5mg/dl rise in serum creatinine levels(18\%); one in the NAC group(4\%) and eight in the non NAC group(30\%)(p<0.05) 24 hours after the injection of contrast medium. In the NAC group mean serum creatinine decreased from 1.94 ± 0.56 to 1.67 ± 0.56 whereas in the non NAC group serum creatinine increased from 1.75 ± 0.31 to 1.98 ± 0.56(p<0.05). Blood urea decreased from 47.58 ± 20 to 41.58 ± 15.1 in the NAC group and increased from 44.96 ± 15.5 to 52.85 ± 20.1 in the non NAC group, but the changes were not statistically significant.

The absolute change in serum creatinine concentration was significantly greater in the non NAC group than in the NAC group .The mean serum creatinine concentration in the NAC group was significantly less than that in the control group 24 hours after the injection of contrast medium.

Calculated creatine clearance increased from 39ml/ min to 45 ml/min in the NAC group and decreased from 41 ml/min to 36 ml/min in the non NAC group.

No significant differences were noted in the levels of sodium and potassium, before and after the procedure in both the groups (Table 2) (Figs.1 and2).

\textbf{Effect of Acetyl Cysteine}

Acute contrast induced reduction in renal function occurred in 9 out of the 51 patients, 1 in the acetyl cysteine group and 8 in the control group. Five of these 9 patients had diabetes mellitus 1 in the NAC group and 4 in the control group.

Presence or absence of diabetes did not affect the therapeutic efficacy of acetyl cysteine.

The patient in the NAC group who developed
contrast-induced reduction in renal function had a baseline creatinine of 1.8 mg%. We could not find any difference in the effect of acetyl cysteine in patients with varying baseline creatinine values, although, control patients with higher baseline creatinine values tended to develop contrast induced nephropathy.

None of the patients required dialysis for renal failure in either group.

**DISCUSSION**

In this study, we found that prophylactic oral administration of the antioxidant acetyl cysteine reduced the incidence of an acute reduction in renal function by contrast agents in patients with abnormal renal function who underwent coronary angiography with or without intervention. Development of contrast-induced renal failure after coronary angiography or intervention, though infrequent, is a serious complication with significant intermediate and long term effects on patient outcome and health care costs.

Incidence of acute CIN in patients with diabetes has been reported to be 50-90% in patients with severe chronic renal insufficiency.\(^{15,16}\) Although many methods were used to prevent acute renal damage by contrast agents, most of the results were disappointing.\(^{7,11}\) How to prevent acute renal damage by contrast agents becomes an important issue, because the application of PCI to the treatment of CAD has grown dramatically since the first balloon angioplasty was performed in 1978. Even small increments in serum creatinine can translate into significant increases in morbidity and mortality.\(^{17}\)

An acute contrast-induced reduction in renal function was defined as an increase in serum creatinine of at least 0.5mg% 24 hours after injection of contrast medium. Such an increase occurred in 18% of our patients, 13.2% and 12% as reported by Shyu et al and Tepel et al. The baseline creatinine values in our patients (1.94 ± 0.56) was relatively less compared to that of Tepel et al (2.4 ± 1.3) and that of Shyu et al (2.8 ± 0.8) but the volume of contrast agent used was larger compared to Tepel et al (110 ± 3ml vs 75ml).

Several previous studies have used antioxidants to reduce acute renal damage in patients undergoing cardiac catheterisation and coronary angiography.\(^{14,18}\) In our patient groups there was a proportionately greater number who underwent angioplasty, which led to a higher volume of contrast usage.

Contrast volume is an important determinant of post procedural renal function. An average contrast volume of 200-350ml has been reported in previous studies of coronary interventions.\(^{1}\) In our study, intervention was performed as an ad hoc procedure and ventriculography was omitted in all the patients. This strategy resulted in a smaller contrast volume of approximately 110 ml. Although our study suggests a protective effect of acetylcysteine during cardiac interventions, this same effect may not be extrapolated to patients who are in need of larger doses of contrast agents.

A simple risk score for prediction of contrast induced nephropathy after PCI has been proposed by Mehran et al.\(^{2}\) which takes into consideration eight variables including hypotension, use of IABP, CHF, CRF, diabetes, age>75 yrs, anemia and volume of contrast used.\(^{40}\)
Postulated mechanisms of action of acetyl cysteine

Potential physiologic effects of acetylcysteine include:
1) It may reduce the ability of generated O2 free radicals to damage cells by scavenging them
2) Increases the expression of nitric oxide synthase in endothelial cells and improves blood flow.
3) Inhibits cell apoptosis

Study Limitations

Limitations of our study include the small sample size, that it is a retrospective analysis and not a prospective randomized study and the fact that it was a single center study, which may reduce the power of the study. Whether different pathologies of renal disease influence the acetylcysteine effect was not explored because the underlying etiology of renal failure in our study was not investigated. Finally the date is limited to 24 hours after the procedure; the effect of acetylcysteine on long term outcomes in patients with abnormal renal function remains unknown.

Clinical Implications

The data presented in this study suggests that the use of acetylcysteine could be beneficial for ameliorating the acute renal failure observed during coronary angiography with or without intervention. The benefit of acetylcysteine seems to encompass all age groups irrespective of the associated risk factors. As suggested by Safirstein et al, because of the low cost of acetylcysteine and its general availability, ease of administration and limited side-effects, the use of acetylcysteine to reduce renal failure induced by contrast agents should be encouraged. However in patients with compromised LV function there is a definite risk of precipitation of LV failure with the infusion of saline for 12 hours prior to and following the procedure.

Enhanced physician awareness of the renal implications of PCI as well as any angiographic procedure involving in vivo injection of contrast agents, in conjunction with careful patient selection, risk assessment and the use of acetylcysteine will help to minimise the incidence of renal failure and the associated increases in morbidity, mortality and healthcare costs.

CONCLUSION

We conclude that prophylactic oral administration of the antioxidant acetylcysteine along with hydration reduces acute renal damage induced by contrast agents in patients with compromised renal function undergoing coronary angiographic procedures. Because of this protective effect the general use of acetylcysteine for this purpose may be warranted.

REFERENCES