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Subtle renal dysfunction after radiocontrast administration in prospective renal donors: Does N-acetylcysteine have a role in its prevention?

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ABSTRACT

Background: Radiographic contrast media (RCM) can cause a reduction in the renal function by multiple mechanisms; reactive oxygen species is one of them. Whether the reduction can be prevented by the administration of antioxidants is still debatable. *N*-acetylcysteine (NAC) has shown some benefit in patients with renal dysfunction in the prevention of radiocontrast-induced nephropathy (RCIN). **Materials and Methods**: We prospectively studied 95 healthy kidney donors, who were undergoing intravenous urography (IVU) followed by digital subtraction renal angiography (DSRA) with ionic, high-osmolar contrast agent for pretransplant evaluation. Patients were randomly assigned either to receive the *N*-acetylcysteine 600 mg orally twice daily (acetylcysteine group) or placebo (control group) on the day before and that of RCM administration in addition to the intravenous 0.45% saline (1 ml/kg body weight per hour) on the day and following day of the procedure. Serum creatinine, urinary enzymes *N*-acetyl β glucosaminidase (NAG), γ glutamyl-1-transferase (GGT), alanine amino peptidase (AAP), fractional excretion of sodium (FeNa) and 24-h urinary creatinine clearance were performed before and 48 h after the procedure. The levels of urinary enzymes measured after 96 h of DSRA were available in only 57 donors. Radiocontrast-induced nephropathy was defined as an increase in the baseline serum creatinine of at least 0.5 mg/dl within 48 h after injection of radiocontrast media (RCM). **Results:** Increase in the urinary enzymes (NAG, GGT and AAP) and reduction in creatinine clearance was observed in both groups after receiving the contrast media. However, the number of patients with significant increase in enzymuria (at least >50% increase above the baseline value) and mean drop in creatinine clearance was statistically not different between the acetylcysteine and control groups. **Conclusion:** Renal damage in the form of reduction in creatinine clearance and increase in urinary enzymes has been observed after administration of radiocontrast. However, clinically significant RCM-induced acute kidney injury is uncommon in patients with normal renal function. Prophylactic oral administration of the antioxidant *N*-acetylcysteine at a dose of 600 mg twice daily before and on the day of contrast administration is probably not required in patients with normal renal function.

Key words: Donor, enzymuria, *N*-acetylcysteine, radio contrast

Introduction

Administration of radiographic contrast agents often results in an acute reduction in the renal function and causes substantial morbidity and mortality during hospitalization in patients with CKD.[1] Contrast agents reduce renal function by imbalance in the arteriolar constriction and dilatation and by exerting direct toxic effects on tubular epithelial cells. Collated evidence suggests that reactive oxygen species have a role in the renal damage caused by contrast agents.[1]

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Studies included in several meta-analyses are heterogeneous with respect to patient population and the type of radiological intervention. Patients with various degrees of renal impairment and comorbid conditions were administered intravenous or intra-arterial radiocontrast at various volumes and different protective doses and routes of administration of *N*-acetylcysteine.[2,3] To circumvent few of these factors, we aimed this study to kidney donors who were going to receive RCM for IVU and DSRA as a part of their routine pretransplant donor evaluation protocol.

NAC may reduce the serum creatinine level without affecting the glomerular filtration rate.[4] Changes in urinary enzyme output reliably reflect the discrete and otherwise undetectable kidney damage.[5,6] Urinary enzymes have been shown to be a sensitive index of

renal tubular damage by radiocontrast.[7] Therefore, we decided to incorporate the estimation of urinary enzymes, namely, NAG-a lysosomal enzyme; GGT and AAP, which are an integral part of the brush border membrane of the proximal tubular epithelium and creatinine clearance to detect smaller magnitude of renal damage by radiocontrast.

In patients with chronic renal insufficiency, hydration has been reported to ameliorate RCIN; however, the administration of drugs such as calcium antagonists, theophylline, dopamine and atrial natriuretic peptide, does not prevent the reduction.[1] Recent attention has been focused on NAC in the prevention of RCIN by virtue of its vasodilatory and antioxidant properties.

Multiple studies have evaluated the impact of NAC against RCIN in patients with renal failure.[8] However, there is a paucity of literature regarding patients with normal renal function who are going to receive RCM. Therefore, we aimed the present study toward evaluating the role of prophylactic oral administration of NAC in a prospective, placebo-controlled, randomized manner involving healthy kidney donors in the prevention of RCIN.

Materials and Methods

Patients

Between July, 2003 and June, 2004, we studied 95 prospective kidney donors with normal renal function. The institution ethics committee approved the study protocol and all patients provided a written informed consent.

Study protocol

The patients were randomly assigned to receive either *N*-acetylcysteine and intravenous saline (acetylcysteine group) or placebo and saline (control group). *N*-acetylcysteine was administered orally at a dose of 600 mg twice daily, on the day before and that of the administration of the contrast agent, for a total of two days. Half-normal saline (0.45%) was intravenously administered at a rate of 1 ml per kilogram of body weight per hour for 12 h before and 12 h after administration of the contrast agent. All patients were encouraged to drink fluid on feeling thirsty. The mean dose of ionic, high-osmolality contrast agent sodium diatrizoate meglumine (75%) was 52.6 ± 10.7 ml (Range: 30–80 ml) for IVU and that of sodium iodide (angiographin, 65%) for renal angiography was 37.6 ± 5.5 ml (Range: 32–50 ml). Renal angiography was performed within 48 h of IVU. During the study, no patients received calcium channel blockers, theophylline, dopamine, mannitol, furosemide and atrial natriuretic peptide. Creatinine Clearance was measured by a 24-h urinary collection method. Urinary enzymes (NAG, GGT and AAP) were measured by spectrophotometric method and expressed as Units/gram of urinary creatinine. FeNa was measured by U/P_{Na} / U/Pcreatinine. All parameters were measured preIVU, 48-h PostIVU, PreAngiography and 48-h postangiography. As mentioned previously, follow-up urinary enzymes after 96-h angiography was available in 57 donors (acetyl cysteine group = 27 and control group = 26).

Statistical analysis

The statistical analysis was conducted by using student's *t* test. P values less than 0.05 was considered statistically significant. Delta method or student's *t* test was used for comparing the difference between two means.

Results

Clinical and biochemical characteristics are shown in Table 1. Both groups were compared for age, gender, body surface area, blood pressure, baseline serum creatinine and creatinine clearance. The mean creatinine clearance, GGT, NAG, AAP and FeNa were studied pre- and postIVU as well as pre- and postrenal angiography in both groups. No significant difference was observed between the two groups at each level for creatinine clearance and GGT. However, NAG at preangiography level and AAP at postangiography level were significantly low in the acetylcysteine group. This has been shown in Table 2.

The means of all parameters were compared preIVU and postDSRA (i.e., before and after receiving the total dose of contrast agent). Creatinine clearance decreased significantly in both groups ($P = 0.04$ and $P = 0.02$ in the control and acetylcysteine group, respectively) and all urinary enzymes increase after the total dose of RCM administration in both groups ($P < 0.0001$). FeNa

Table 1: Clinical and biochemical characteristics of the study patients

	Control	Acetylcysteine	*P*-value
Age	42.20 ± 10.18	38.73 ± 10.24	NS*
Gender (M/F)	31/20	31/13	NS*
Body surface area (m^2)	1.62 ± 0.22	1.61 ± 0.16	NS*
Systolic blood pressure (mmHg)	132.6 ± 14.7	134.6 ± 13.8	NS*
Diastolic blood pressure (mmHg)	81.8 ± 8.1	82.5 ± 6.3	NS*
Serum creatinine (mg/dl)	0.75 ± 0.14	0.74 ± 0.12	NS*
Creatinine clearance (ml/min/1.73 m^2)	105.41 ± 30.38	106.66 ± 22.89	NS*

NS* = Not Significant

Table 2: Comparison between two groups at all levels

	Group	PreIVU	PostIVU	Preangiography	Post angiography
Creatinine clearance (ml/min/1.73m^2)	Control	105.41	100.77	98.62	94.94
	Acetylcysteine	106.66	101.42	100.94	96.22
	P value	0.41	0.45	0.33	0.41
γ Glutamyl-1-transferase (GGT; U/g urinary creatinine)	Control	19.15	37.59	24.76	35.98
	Acetylcysteine	19.09	33.01	22.01	32.53
	P value	0.48	0.08	0.15	0.10
N-acetyl β glucosaminidase (NAG; U/g urinary creatinine)	Control	2.18	4.07	3.03	4.72
	Acetylcysteine	2.23	3.45	2.30	4.04
	P value	0.43	0.08	0.03	0.13
Alanine amino peptidase (AAP) (U/g urinary creatinine)	Control	2.99	6.55	4.49	7.61
	Acetylcysteine	3.46	5.63	3.69	5.90
	P value	0.07	0.06	0.08	0.005
Fractional excretion of sodium (FeNa) (%)	Control	0.80	1.01	0.85	0.88
	Acetylcysteine	1.06	1.18	0.96	0.81
	P value	0.02	0.16	0.22	0.25

significantly decreased only in the acetylcysteine group ($P = 0.03$). However, the mean decrease in creatinine clearance was not significantly different between the two groups as highlighted in Fig. 1 ($P = 0.50$). Similar scenario was noticed for GGT ($P = 0.10$) and NAG ($P = 0.10$). Only AAP increased significantly less in the acetylcysteine group ($P < 0.0001$) as shown in Fig. 2. When the number of patients who had significant increase in urinary enzymes, that is, at least >50% above the basal value were compared between the two groups, no significant difference was noted. This has been shown in Table 3. All Urinary enzymes returned to almost baseline values after 96 h of DSRA. The course of all urinary enzymes, including GGT, NAG and AAP before and after IVU and angiography, in both groups is highlighted in Figs. 3–5, respectively.

Table 3: Number of patients with significant enzymuria (>50% above the basal value)

	GGT (U/g urinary creatinine)	NAG (U/g urinary creatinine)	AAP (U/g urinary creatinine)
Control (n = 51)	35	36	37
Acetylcysteine (n = 44)	27	28	25
P value	0.59	0.61	0.16

Discussion

An important finding of the present study is that administration of contrast agent causes renal damage that is reflected by decrease in creatinine clearance and increase in enzymuria and reversal of increase in enzymuria after 96 h of renal angiography. Prophylactic oral administration of the antioxidant *N*-acetylcysteine did not help in preventing the reduction of creatinine clearance and increase in enzymuria.

Patients receiving radiocontrast agents are at a risk for developing RCIN, which accounts for 10% of all causes. In fact, RCIN is currently the third leading cause of hospital-acquired acute renal failure.[9]

Patients with RCIN typically present with an acute increase in serum creatinine anywhere between 24 and 48 h. It peaks around 3–5 days and eventually returns to the baseline value within 7–10 days. Most cases of RCIN are reversible and nonoliguric in nature. However, permanent decline in the renal function following contrast administration may be observed in approximately 30% of patients.[10]

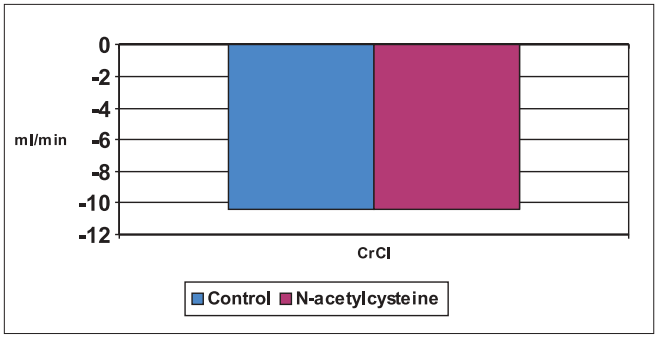

Fig. 1: Reduction in creatinine clearance after RCM administration

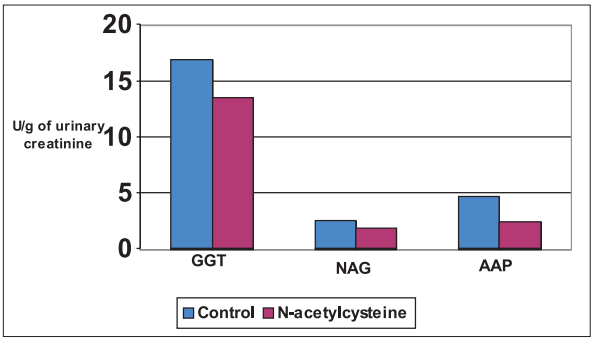

Fig. 2: Comparison of means before and after RCM administration

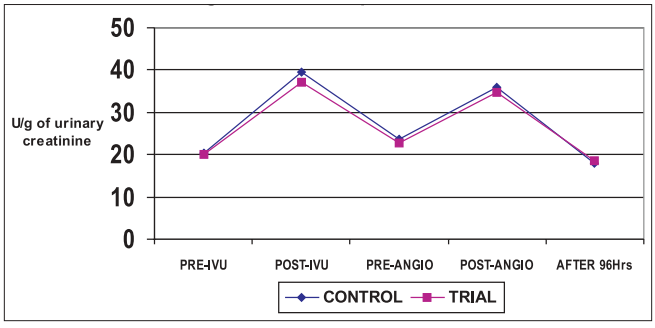

Fig. 3: Follow-up of GGT

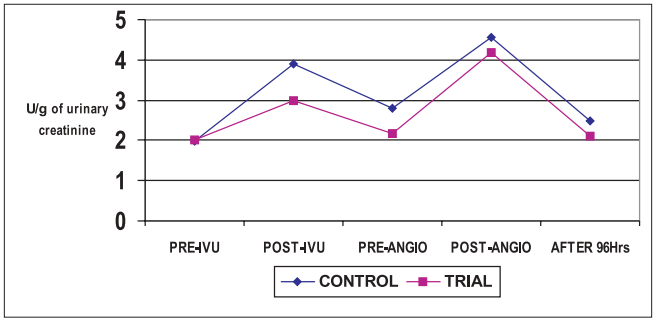

Fig. 4: Follow-up of NAG

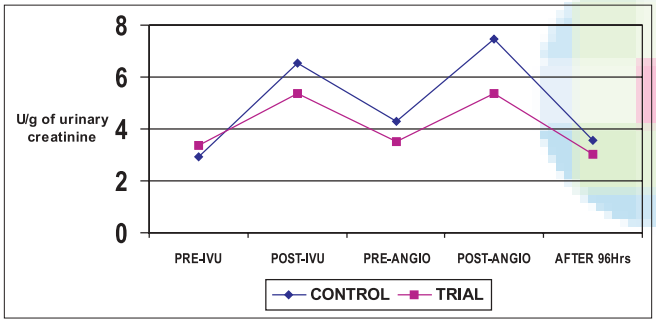

Fig. 5: Follow-up of AAP

Important risk factors for RCIN are preexisting renal dysfunction, particularly that caused by diabetic nephropathy; reduced effective arterial volume; concomitant administration of drugs that interfere with the regulation of renal perfusion, such as angiotensin-converting-enzyme inhibitors; and a higher volume of contrast agent administered.[1] Of all these risk factors, preexisting renal failure appears to be the single most important risk factor.[10]

RCIN is believed to result from a combination of direct renal tubular epithelial cell toxicity and renal medullary ischemia. Moreover, as stated previously, reactive oxygen species do play a role in the generation of RCIN. In addition, alterations in the metabolism of NO, adenosine, endothelin, Ang II and prostaglandin may also play pivotal roles in the development of RCIN.[10]

One of the characteristics of the kidney is its ability to compensate for damage, and for this reason classical kidney function tests are insensitive since they deviate when there is a large reduction in the effective nephron mass.[5] It has also been observed with RCM that renal effects are often not detected by the means of conventional renal function tests. On the contrary, urinary excretion of various enzymes appears to be very sensitive to RCM. The close contact between the tubular urine, containing filtered RCM and the tubular epithelial cells where these enzymes are located, may explain the high sensitivity of these enzymes to the administration of RCM.[6]

Various approaches have been attempted to abrogate the contrast-induced injury. Among the list of therapies with good clinical evidence are fluid administration and *N*-acetylcysteine.[1] Mixed results have been shown by studies conducted with fenoldopam[11] and theophylline,[1] while studies carried out using calcium channel blockers, diuretics, mannitol, dopamine, atrial natriuretic peptide, endothelin antagonist, prostaglandin E and angiotensin-converting enzyme inhibitor showed conflicting results.[11]

NAC is a thiol-containing antioxidant compound, which reduces the ability of the generated oxygen free radicals to damage cells by scavenging them. It also increases the biological effects of NO by combining with NO, forming S-nitrosothiol, which is a more stable form and a potent vasodilator. These interactions may also limit the production of the damaging peroxinitrite. NAC also increases the expression of NO synthase and may thus improve blood flow as well. Thus, acetylcysteine promotes pathways that lead to the repair and survival whenever cells are under oxidant stress.[12]

Several meta-analyses of randomized trials could not show the consistent benefit of NAC in patients with underlying renal insufficiency.[2,3,9] Tepel and colleagues randomized 83 patients to receive either NAC (600 mg bid on the day before and day of contrast administration) or a placebo. The incidence of RCIN was significantly lower in patients who received NAC as compared to placebo (2% v/s 21%, $P<0.01$).[1] Shyu and colleagues randomized 121 high-risk patients to either NAC or a placebo with hydration. Incidence of RCIN was significantly low in the NAC group as compared to placebo (3.3% v/s 24.6%, $P < 0.001$).[11] Kay and colleagues also showed significant reduction in RCIN in the NAC group compared to placebo (4% v/s 12% P 0.03).[11] However, Brigouri *et al.*, could not find any added advantage of NAC as compared to

placebo in 183 patients.[11] Allaquaband *et al.*, also found same results.[11]

Majority of the studies with NAC were conducted on patients with compromised renal function. There is paucity of literature in patients without renal insufficiency. It is believed that a patient with normal renal function prior to RCM has very low risk of developing renal failure. In the present study, we aimed to assess the effect of RCM in normal healthy kidney donors and the effect of NAC in prevention of RCIN. Although the reduction in creatinine clearance and increase in urinary enzymes were observed after radiocontrast administration, we did not find any episode of clinically significant acute kidney injury. Moreover, significant increase in urinary enzymes and mean reduction in creatinine clearance were not different between the acetylcysteine and placebo groups.

Conclusion

Radiocontrast administration causes renal damage as observed by reduction in creatinine clearance and increase in enzymuria. However, clinically significant RCM-induced acute kidney injury is uncommon in patients with normal renal function. Prophylactic oral administration of the antioxidant *N*-acetylcysteine at a dose of 600 mg twice daily before and on the day of contrast administration is probably not helpful in patients with normal renal function.

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