The effect of oral N-acetylcysteine on serum creatinine in chronic kidney diseases patients under CABG surgery

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Abstract: Background: Many researches show risk factors of cardiac disease in individuals suffering from chronic kidney disease(CKD).In CKD patients who are candid CABG, there are great concerns about acute kidney injury. Iincrease in serum Creatinine is associated with increase in morbidity and mortality in CAGB patients. Therefore, purpose of this study is investigating serum creatinine variation and GFR after oral NAC injection in CKD patients who are candid for CABG. **Material and Method:** 50 patients candid for CAGB were selected in blind design randomized, clinical trial in Golstan and Imam' hospitals in Ahvaz during 2010-2011. All patients had nephropathy type 2 based on kidney fund classification and had diagnostic criteria for chronic kidney diseases or it lasts for three months (GFR<90, Cr>1.5).Intervention group received 600mg oral NAC twice a day from one day before surgery to 5 days after surgery through esophagus catheter and control group received distilled water with same amount and volume. Finaly the serum creatinine, GFR and some other factors were measured. **Results:** There is a significant difference inserum creatinine(P=0.002), GFR(P=0.002) and BUN (P=0.034)between control and intervention groups after 5days. **Conclusion:** Results of this study and its comparison with other studies showed great disagreement about effect of NAC on serum creatinine but considering lack of side effects or severe changes in serum creatinine in NAC receiving patients, it can be used as a safe drug.
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Key words:N-acetylcysteine, serum creatinine, GFR, chronic kidney diseases(CKD), CABG

Introduction

Cardiac and kidney failure diseases are increasing everyday [1] and evidences show that failure in kidney function leads to cardiac failure and vice versa [2]. Many researches show risk factors of cardiac disease in individuals suffering from chronic kidney disease(CKD) [3-4] and it is observed that kidney diseases increase cardiovascular diseases, mortalities and morbidities [5] such that we can say patients suffering from CKD will die as a result of cardiovascular diseases not advanced kidney failures [6] because rate of stroke in CKD patients is high and can lead to death related to cardiovascular diseases [7] and it is estimated that 13% of CKD patients suffer from myocardial stroke [8-9]. In CKD patients who are candid for coronary artery bypass grafting (CABG), there are great concerns about acute Kidney failure and rate of acute kidney injury (AKI) after cardiac surgery varies from 1-3% dependent on patients' characteristics [10]. Various studies have reported that increase in serum Creatinine is associated with increase in morbidity and mortality in CAGB patients under pump [11] and slight increase in serum Creatinine leads to cardiovascular injuries and stroke [12]. Reports indicated that increase in serum creatinine is seen in 20-40% of patients hospitalized because of cardiac failure[13-15]. Creatinine is used for estimating glomerular filtration rate (GFR) [16] and one of risk factors in cardiovascular diseases in CKD patients is reducing GFR after increasing serum creatinine [17]. Results of researchers show that there is difference about dependence or independence of serum creatinine variations relative to GFR [18-21] because serum creatinine is influenced by factors like age, gender, race and body mass index and it is necessary to consider these important factors to understand relationship between increasing Creatinine and reducing GFR with accurate information and development of cardiovascular diseases [22]. Reports indicate that increase in serum creatinine increases morbidity, mortality, hospitalization, return to hospital and costs [23-26]. N-acetylcysteine (NAC) is studied for preventing kidney injury and in this study

serum creatinine variation was controlled for evaluating GFR [27]. It is necessary to mention that one of important mechanisms for kidney injury is oxidative stress [28] and NAC is a sulfhidril-containing compound which has strong anti-oxidative features [29]. NAC is suitable for cardiac function improvement after myocardial stroke [30]. Studies have stated that NAC can reduce serum creatinine [31] but instead of these studies NAC has a contrasted history about preventing kidney injuries [32-33] and even reduction in serum creatinine after NAC injection was debated by researchers [34-35]. Therefore, purpose of this study is investigating serum creatinine variation and GFR after oral NAC injection in CKD patients who are candid for CABG.

Methods: after approval of ethic committee in by Ahvaz Jundishapur University of Medical Sciences and consent form signed by participants, 50 patients candid for CAGB were selected in blind design randomized, clinical trial in Golstan and Imam' hospitals in Ahvaz during 2010-2011. All patients had nephropathy type 2 based on kidney fund classification and had diagnostic criteria for chronic kidney diseases or it lasts for three months (GFR<90, Cr>1.5). Patients who had dialysis before surgery or emergency operation or kidney implant or received contrast drug one week before study were excluded from the study. Other patients were assigned randomly to groups receiving NAC and placebo. Intervention group received 600mg oral NAC twice a day from one day before surgery to 5 days after surgery through esophagus catheter and control group received distilled water with same amount and volume. Patients received 0.1mg/kg intramuscular morphine and 25mg promethazine. They consumed their heart drug until the day before surgery (except ACE-I). Patients received intravenous prophylactic antibiotic Cephazoline 1.5g in each 8 hours until 24 hours. Analgesic drugs initiated with thiopental 2-3 mg/kg and phentanil (3-5 mg/kg) and Atrachorim (0.5mg/kg) and midazolam (0.1mg/kg) for EKG and CVP and patients were monitored. Circular membrane oxygenator was used. Prime solution was given with 1 liter normo-smolar ringer, 500cc glucose and one vial bicarbonate and 100cc manitol were given before surgery. Flow rate was determined such that average blood pressure was 60-80 mmHg. In connecting to CPB, before recovery and 2 hours after surgery systolic blood pressure, diastole, heart rate, CVP, PaO2, artery pH and SaO2 were measured and recorded. Blood pressure measurement was done invasively. CVP was evaluated with pressures. Blood gases including PaO2, pH and Sao2 were measured. Patients were measured for connecting membrane. When systolic blood pressure was lower than 90mmHg, Intrope was injected with 0.1-0.01ug/kg/min. additional ringer was used to maintain stable fluid level. Hemodilation was done to keep 7g/dl Hg. Myocardial monitoring with forward and backward Cardoiplagy was done with cold blood. After surgery all contents were returned to patients. After surgery patients was transferred to ICU to sedate and prophel was injected for re-warming. In the case of homodynamic stability and pain control patient was removed from mechanical ventilation. Hemodynamic management in patients includes keeping MAP>65 with crystalloid and Cloido-infusion Dopamine and epinephrine were injected, when necessary.

Results:

Results of study showed that primary characteristic of patients in study and their histories in both control and intervention group had not significant differences with each other (table 1). Data analysis indicated that cardiac EF of both groups had no significant differences (P=0.164). Mean total bypass time was 72.72+/-16.35 for control group and 88.40+/-12.88 for intervention group. This time had significant differences between both groups (P=0.003). from BUN concentration comparison we can show that using NAC will significantly decrease BUN in CABG surgery (P=0.034). This reduction in concentration in intervention group is higher than control group. Comparing Na, K, HCO_3 concentration between both control and intervention groups in different times showed insignificant differences between both groups and we can conclude that using NAC has not significant effect on Na, K and HCO3 concentration in CABG patients. Based on Freidman analysis there was a significant statistical differences in creatinine variation one day before surgery to 5 days after surgery in control group such that mean creatinine was increased from 1.60 mg/dl to 1.90 mg/dl in day 0. Based on this test, there was a significant difference in creatinine variation form one day before surgery and 5 days after surgery such that its mean reduced from 1.80 mg/dl to 1.40 mg/dl. Based on Mann-Whitney test there is a significant difference between creatinine in day 5 between control and intervention groups (P=0.002). Mean creatinine was increased in control group but decreased in intervention group (figure 1). Based on this test, there is a significant difference between groups from day 5. Based on Friedman test, there is a significant statistical difference between GFR from one day before surgery to 5 days after surgery in control group such that mean GFR was reduced from 47.03 in day 0 to 41.62 ml in minutes. Based on this test there was a significant statistical difference between GFR from day 1 before surgery to 5 days after surgery in intervention group such that

median GFR increased from 40.70 in day 0 to 51.90 ml in minutes (figure 2).

Discussion

CKD patients cannot participate in clinical trials because there are great concerns about side effects of drugs and methods but it is clear that there is a need for more studies to increase life quality of these patients. As results of this study show, changes in serum creatinine has increased in control group but decreased in intervention group and caused GFR difference between both groups such that mean GFR increased in intervention group but decreased in control group. Adabag(36) et. al, by studying effect of oral NAC on AKI prevention after cardiac surgery, had reported that serum creatinine in NAC group has increases 0.45+0.7mg/dl but 0.55+0.9mg/dl in control group, but this difference in not significant and serum creatinine increase in NAC group in this study was lower than control group(P=0.53). Staniloae (37) et. al in a study on NAC effects on preventing nephropathy caused by contrast in angiography patients with kidney failures showed that serum creatinine was increased in 4.2% intervention group patients while in control group 6.5% patients had increase in serum creatinine but this was not significant (P=0.38). But like our study increase in serum creatinine was lower in intervention group.

Table 1. Preoperative characteristics (No Statistically Significant Difference) COPD: chronic obstructive pulmonary disease, MI: myocardial infarction

Variable	Control group (n = 25)	Nacetylcysteine group (n = 25)	P Value
Age	63.28+8.21	62.041+8.62	0.651
Male sex	20(80.0)	22(88.0)	0.702
Weight	75.1614.04+	70.80+12.52	0.317
Stature	165.44+7.49	164.44+9.09	0.846
Hypertension	15(60.0)	13(52.0)	0.776
Diabetes	11 (44.0)	10(40.0)	1.000
Hyperlipidemia	14(56.0)	17(68.0)	0.561
COPD	1(4.0)	5(20.0)	0.189
Vascular disease	3(12.0)	0	0.235
Stroke	3(12.0)	0	0.235
MI	11(44.0)	15 (60.0)	0.396

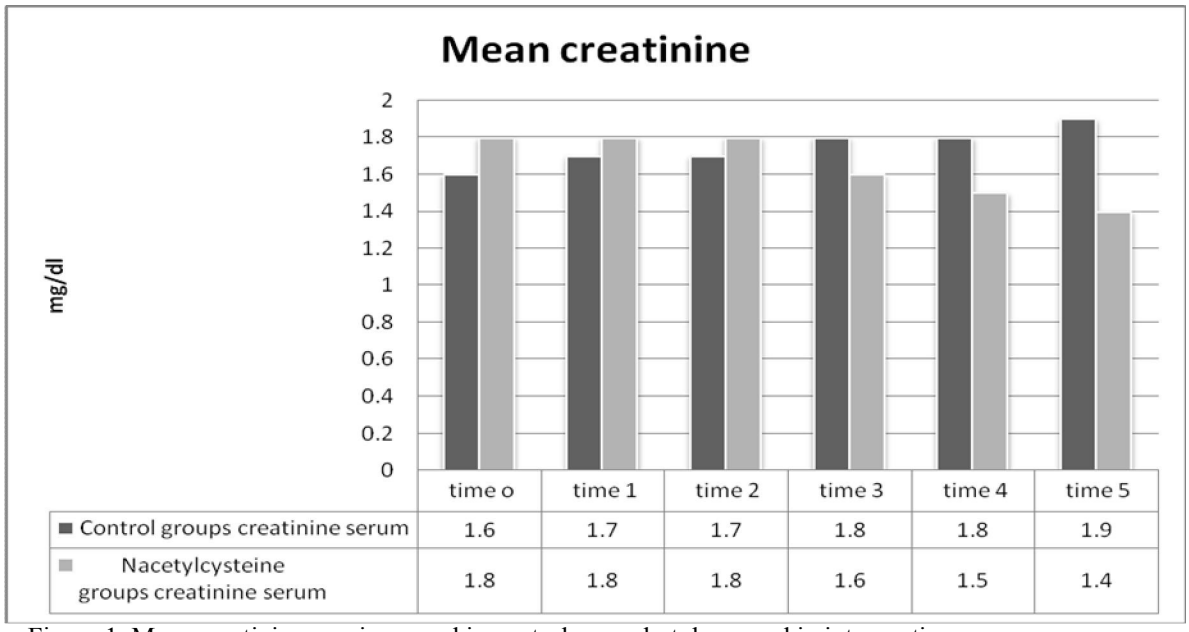

Figure 1. Mean creatinine was increased in control group but decreased in intervention group

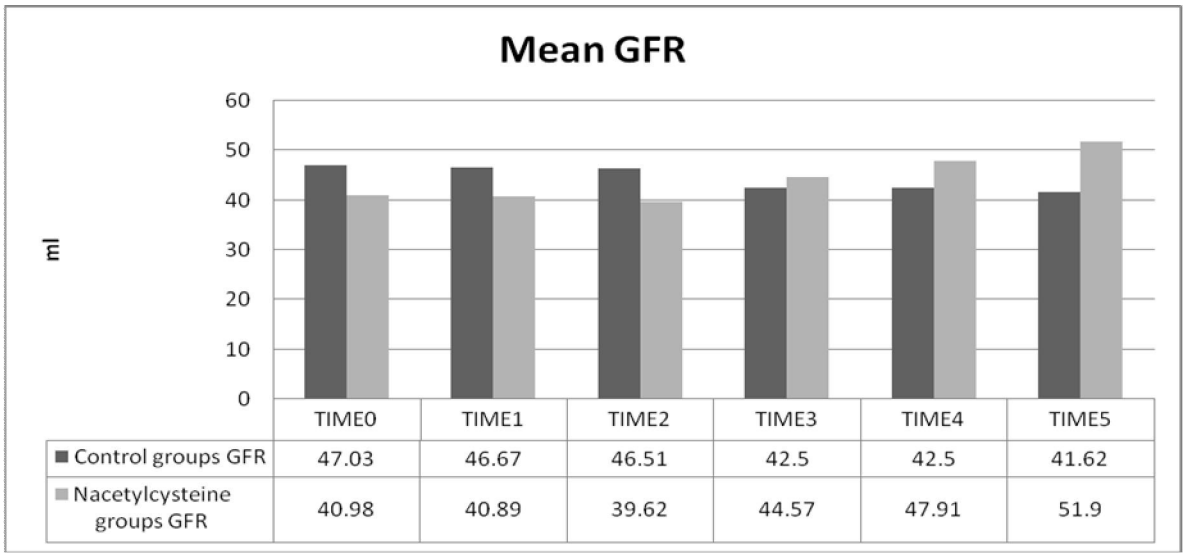

Figure 2. Based on this test there was a significant statistical difference between GFR from day 1 before surgery to 5 days after surgery in intervention group such that median GFR increased from 40.70 in day 0 to 51.90 ml in minutes

Following other studies we reach other results such that Wesner (38) et. al in their study "effect of oral NAC injection before surgery on postoperative blood lose, indicated that mean serum creatinine variances in intervention and control groups was not significantly difference in recharge relative to base line (p=0.769) but in their studies, mean serum creatinine variances in intervention group increased 0.001+0.211mg/dl but 0.004+0.175mg/dl in control group which in contrast with our study, in their study NAC increases serum creatinine which was not significant. In other study Burns(39) et. al studied effect of perioperative NAC drug effect on kidney failure in high risk CABG patients and showed that in 29.7% of NAC receiving group serum creatinine was increased but in control group 29% had increase which was not significant (p=0.89). Webb(40) et. al, by studying effect of NAC on preventing nephropathy caused by contrast in cardiac catheterization, showed that in NAC group 7.3% patients had increase in serum creatinine while this increase occurred in 5.7% patients in control group and in their study, NAC has increased serum creatinine but was not statistically significant(p=0.57) and contrasted with our results. It is necessary to mention that in this study we have investigated effect of NAC on other factors like HCO3, K, Na and BUN which had significant difference in BUN. Therefore, it is suggested that other studies investigate creatinine variation and other factors like BUN.

Conclusion:

Results of this study and its comparison with other studies showed great disagreement about effect of NAC on serum creatinine and certain decision-making is not possible, but it is suitable considering lack of side effects or severe changes in serum creatinine in NAC receiving patients.

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