N-acetylcysteine for Prevention of Postoperative Renal Failure

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Several pharmaceutical agents have been proposed as protective factors against acute renal failure, from which N-acetylcysteine gained a particular interest. The aim of the current research is to evaluate NAC ability of preventing ARF in patients with chronic kidney disease (CKD) undergoing coronary artery bypass grafting (CABG). The authors analyzed 92 patients with preoperative CKD that benefited from CABG between 2000-2010. 44 of the 92 patients received intravenous NAC immediately after cardiopulmonary bypass cessation while the remaining 48 patients did not receive any particular medication. Postoperatively, estimated glomerular filtration ratio (eGFR) decreased with 14.73% in patients that did not receive NAC and with 13.1% in patients that received NAC (p = 0.07). From the 14 patients that required hemodialysis, 6 received NAC (13.67%) and 8 did non receive NAC (16.67%) (p = 0.55). ICU admission was similar for the two groups of patients (8.71 days in NAC group and 8.52 days in the no NAC group) (p = 0.15). The 2 patients with CKD that did not survive the first 30 days were not treated with NAC. No adverse effects to NAC and no statistically significant difference concerning the incidence of postoperative complications were noticed in the study group. Thus, the results of the current study suggest that NAC administration in patients with CKD brings little to no benefit in the prevention of postoperative ARF.

Keywords: N-acetylcysteine, pharmaceutical agents, oxidative stress, glutathione, cysteine, estimated glomerular filtration ratio

Studies all over the world proposed many pharmacological agents like dopamine, furosemide, calcium channel antagonists, angiotensin-converting enzyme inhibitors, atrial natriuretic peptide, fenoldopam, N-acetylcisteine (NAC) ($C_5H_9NO_3S$) as protective agents against acute renal failure [1].

At first, NAC was used as a mucolytic agent based on its property of splitting disulfide connections between mucus glycoproteins and as a cysteine substrate for the restoration of hepatic glutathione in case of acetaminophen intoxication that is metabolized into N-acetyl benzoquinoneimine, a substance that depletes hepatic glutathione ($C_{10}H_{17}N_3O_6S$) stores.

Acute renal failure (ARF) is a severe complication of cardiac surgery with a reported incidence between 1% and 30% and severe ARF requiring dialysis occurs in 1-5% of cases [2]. Despite the improvement of surgical techniques and postoperative management in intensive care units (ICU), postoperative ARF is still associated with a high mortality rate ranging between 15 to 30% [3].

ARF occurring after cardiac surgery can be attributed to acute tubular necrosis in a majority of cases, although multifactorial origin can also be detected. Several risk factors have been identified, but the most important are preexisting chronic kidney disease (CKD), advanced age, diabetes mellitus, exposure to nephrotoxic agents (especially iodinated contrast material), and prolonged cardiopulmonary bypass (CPB). Thus, high-risk patients can be identified prior to surgery and prophylactic measures can be adopted in order to prevent kidney injury [3].

Cardiac surgery associated ARF is mainly caused by increased oxidative stress and renal glutathione depletion secondary to ischemia reperfusion injury. NAC, an acetylated derivate of cysteine ($C_3H_7NO_2S$), acts as an antioxidant agent and inductor of glutathione synthesis by providing the necessary cysteine substrate for intracellular glutathione synthesis (fig. 1). Additionally to the above-mentioned properties, NAC has a vasodilatory effect by stabilizing the nitric oxide (NO) and inhibiting the angiotensin-converting enzyme through its sulfhydryl group thus preventing renal vasoconstriction, another factor contributing to ARF. Heyman et al. proved on animal studies that NAC reduces renal vascular resistance with up to 10% [4].

The aim of the current research is to evaluate NAC ability of preventing ARF in patients with CKD undergoing coronary artery bypass grafting (CABG).

Experimental part

Materials sand methods

The authors performed a retrospective case-control research on 92 patients with CKD out of the 1148 patients that underwent CABG at the Institute of Cardiovascular

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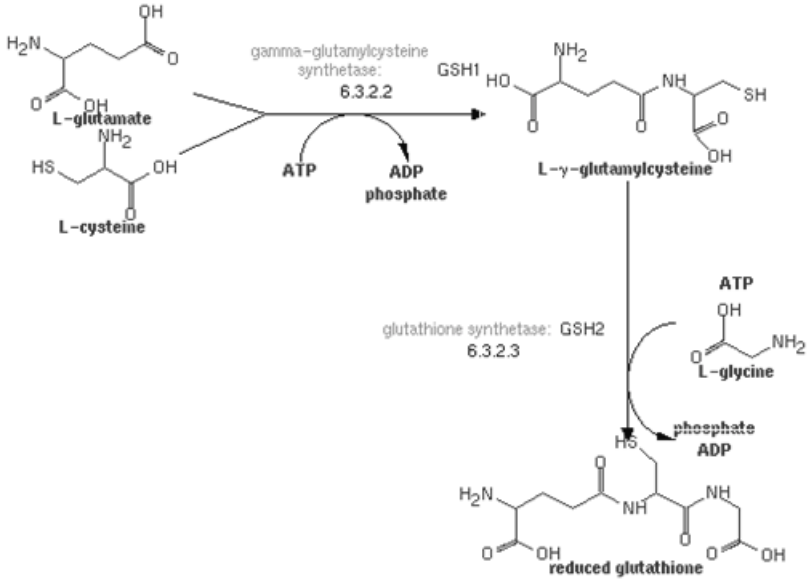

Fig. 1. Glutathione synthesis from cysteine

Diseases from Iasi, Romania, between 2000-2010. Out of the 92 patients, 44 received NAC postoperatively.

Preoperative, intraoperative and postoperative data was analyzed in a comparative manner in terms of short-term prognosis (ARF, in hospital morbidity and mortality).

Preoperative CKD was affirmed in cases with estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73m^2 or documented chronic renal impairment based on nephrologic evaluation. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula:

$$eGFR\,(mL/min/1.73\,m^2) = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if Afro American})$$

where S_{cr} = serum creatinine

The surgical procedure was conducted under standard CPB. All patients benefited from on-pump CABG with or without additional procedures (valve repair, valve replacement, ventricular aneurysm resection, mixoma excision, atrial septal defect closure, aortic procedures).

The extracorporeal circulation (ECC) protocol in patients with CKD aimed to provide optimal kidney perfusion by maintaining the mean blood arterial pressure above 70-80 mmHg. Ultrafiltration during heating maneuvers was performed in case of hematocrit <22%, refractory to transfusions, suboptimal diuresis or in patients with chronic hemodialysis. 44 patients received NAC, 100 mg/kg in intravenous bolus or 20 mg/kg/h in intravenous infusion, immediately after CPB.

The postoperative protocol for all patients with CKD included hourly monitoring of diuresis and creatinine dynamics, avoidance of nephrotoxic medication, hemodynamic stability (maintaining appropriate arterial pressure and heart rate values, avoidance of heart rhythm disturbances). Hemodialysis was initiated in the following cases: doubled creatinine values related to preoperative status, diuresis below 0.5 mL/kg/hour, diuresis nonresponsive to diuretic treatment, hiperkalemia nonresponsive to treatment.

In-hospital postoperative ARF, morbidity and mortality were defined as occurring within 30 days from surgery.

MedCalc software (version 12.1.3; MedCalc Software, Mariakerke, Belgium) was used for statistical analyses. Continuous variables were expressed as the mean ± standard deviation (SD). Analysis of variance was used to compare continuous variables, and we used the chi-square test for categorical variables. For all analyses, a P value <0.05 was considered statistically significant.

Results and discussions

Out of the 1148 patients undergoing CABG in the studied period, 92 (8.01%) had CKD. Preoperative demographic and clinical features of patients are presented in table 1. Patients with CKD were older, had higher rates of arterial hypertension and diabetes mellitus, peripheral artery disease, carotid artery disease, cerebrovascular diseases; more severe cardiac failure according to New York Heart Association (NYHA) class, and a higher prevalence of three-vessel disease. Tourniquet test was used in 12 patients in order to preoperatively determine the presence of clinically manifested hypocalcemia.

Parameter	CKD	No CKD	*P*
Age (years)	64.36±7.89	59.86±9.08	<0.0001
Female sex, n (%)	13 (14.13%)	190 (17.99%)	0.35
Left ventricular ejection fraction (LVEF), %	52.58±11.08	53.34±10.93	0.58
Arterial hypertension (AHT), n (%)	77 (83.69%)	678 (64.2%)	0.0001
Diabetes mellitus (DM), n (%)	38 (41.3)	282 (26.7)	0.002
Creatinine, mmol/L	120±48.98	78.87±15.96	<0.0001
Peripheral vascular disease, n (%)	15 (16.3)	36 (3.4)	<0.0001
Carotid artery disease, n (%)	15 (16.3)	76 (7.19)	0.001
Cerebrovascular disease, n (%)	19 (20.65)	11 (1.04)	<0.0001
NYHA class III-IV	38 (41.3)	72 (6.81)	<0.0001
Previous acute myocardial infarction (AMI), n (%)	40 (42.47)	426 (40.34)	0.55
Triple vessel disease, n (%)	65 (61.55)	450 (42.61)	<0.0001
EuroScore, %	4.48±3.8	3.78±2.4	0.01

Table 1
PREOPERATIVE PARAMETERS

Parameter	CKD	No CKD	*P*
Average number of distal anastomosis, n	2.89±1.14	2.63±1.04	0.01
Average number of arterial grafts, n	1.53±1.06	1.65±1.08	0.32
Average number of venous grafts, n	1.6±1.05	1.2±1.1	0.005
Average ECC time, min	143.63±42.39	140.22±57.12	0.44
Additional cardiac procedures, n (%)	28 (30.43)	248 (23.48)	0.13

Table 2
INTRAOPERATIVE PARAMETERS

Parameter	CKD	No CKD	*P*
Global mortality, n (%)	2 (2.17)	14 (1.32)	0.5
Dialysis, n (%)	14 (15.21)	16 (1.51)	<0.0001
Average ICU stay, days	8.56±6.74	6.53±3.78	<0.0001
Average mechanical ventilation time, hours	26.85±56.42	15.36±44.56	0.02
Total hospital stay, days	25.29±10.6	19.15±11.17	<0.0001
Multiple organ dysfunction syndrome (MODS), n (%)	6 (6.52)	14 (1.32)	0.0002
Reoperation for hemorrhage or sternal dehiscence, n (%)	16 (17.39%)	92 (8.71%)	<0.0001
Atrial fibrillation, n (%)	42 (45.65)	220 (20.83)	<0.0001
Infectious complications, n (%)	12 (13.04)	39 (3.69)	<0.0001

Table 3
POSTOPERATIVE PARAMETERS

Patients with CKD had more distal anastomosis and there were no statistically significant differences regarding the need for additional cardiac procedures and average extracorporeal circulation (ECC) time (table 2).

Concerning the postoperative outcomes, there was no significant difference regarding in-hospital mortality between patients with and without CKD, but ICU admission, average postoperative mechanical ventilation time, and certain complication rates were higher in patients with CKD (table 3).

Afterwards, the outcomes of patients with CKD that received NAC (test group) were compared with those of the patients that did not receive NAC postoperatively (control group). Preoperative and intraoperative parameters were similar between the two groups (table 4).

Postoperatively, eGFR decreased with 14.73% in patients that did not receive NAC and with 13.1% in patients that received NAC ($p = 0.07$). From the 14 patients that required hemodialysis, 6 received NAC (13.67%) and 8 did (16.67%) ($p = 0.55$). ICU admission was similar for the two groups of patients (8.71 days in NAC group and 8.52 days in the no NAC group) ($p = 0.15$). The 2 patients with CKD that did not survive the first 30 days were not treated with NAC. No adverse effects to NAC and no statistically significant difference concerning the incidence of postoperative complications were noticed in the study group. Thus, the results of the current study suggest that the administration of NAC in patients with CKD brings little to no benefit in the prevention of postoperative ARF.

CKD is a recognized risk factor for premature atherosclerosis. The revascularization method of choice in these patients is still controversial. Several studies have shown that coronary artery bypass grafting is associated with higher procedural death, but better long-term survival compared to percutaneous coronary intervention [5, 6].

The current study demonstrates that CKD is common in patients undergoing CABG. We found a prevalence of CKD of 8.01%, which is similar to other previous studies [7, 8], but is considerably higher than data reported in the 4th European Association for Cardiothoracic Surgery Adult Cardiac Surgery Database Report (<2%) [9].

Patients with CKD have a higher prevalence of comorbidities and risk factors such as advanced age, diabetes mellitus, peripheral arterial disease, cerebrovascular disease, congestive heart failure and, thus, a higher EuroScore, findings similar to other studies [10].

In our study group, there were no statistically significant differences when comparing intraoperative parameters between patients with and without CKD except for the number of distal anastomosis that was higher in patients with CKD due to a more extensive coronary arteries disease.

All interventions were performed using CBP, a technique associated with low perfusion pressures, non-pulsatile flow, and the release of inflammatory mediators; factors involved in the development of ARF [5]. In a retrospective study of 158 patients from the STS (Society of Thoracic Surgeons) database, the use of CPB was an independent risk factor for early perioperative death in case of patients with end-stage kidney disease [11]. Contrastingly, in a larger

Parameter	NAC	No NAC
Age (years)	64.81±8.12	63.02±9.01
Female sex, n (%)	6 (13.63)	7 (14.58)
NYHA class III-IV	18 (40.91)	20 (41.67)
Left ventricular ejection fraction (LVEF), %	51.78±12.17	52.75±10.61
Creatinine, mmol/L	125±45.73	117±43.36
eGFR 30-60 mL/min/1.73m^2 (moderate CKD), n (%)	37 (84.09)	40 (83.33)
eGFR <30 mL/min/1.73m^2 (severe CKD), n (%)	7 (15.91)	8 (16.67)
Diabetes mellitus (DM), n (%)	17 (38.64)	21 (43.75)
Peripheral vascular disease, n (%)	6 (13.64)	9 (18.75)
Carotid artery disease, n (%)	7 (15.91)	8 (16.67)
Cerebrovascular disease, n (%)	10 (22.73)	9 (18.75)
Average ECC time, min	143.11±38.81	145.02±49.15
Additional cardiac procedures, n (%)	13 (29.55)	15 (31.25)

Table 4
PREOPERATIVE AND INTRAOPERATIVE PARAMETERS OF PATIENTS WITH CKD DEPNDING ON NAC ADMINISTRATION

study of the USRDS database, perioperative mortality was similar both in patients undergoing off-pump and on-pump coronary artery bypass [12]. In our study group the <30 days mortality rate was low and statistically acceptable no matter the presence of CKD and usage of CPB.

Mortality in the studied CKD group was smaller than the one reported by other researches (2.2-7.1%) [13]. However, patients with CKD experienced significantly higher rates of postoperative complications: atrial fibrillation, infectious complications, re-intervention due to bleeding or sternal dehiscence, MODS, prolonged mechanical ventilation and ICU stay. In our study group, 15.21% of CKD patients required postoperative dialysis.

The pathogenesis of ARF after cardiac surgery involves a complex interaction between preoperative CKD or other risk factors (diabetes mellitus, severe heart failure), intraoperative and postoperative factors. Ischemia-reperfusion injuries, increased oxidative stress, release of systemic inflammation cytokines during cardiac surgery play a crucial role in the development of postoperative ARF [1]. Theoretically, after showing promising results in *in vitro* and *in vivo* animal studies [14], NAC has the potential of being useful in preventing ARF by neutralizing free radicals, reducing proinflammatory cytokines and increasing kidney glutathione synthesis.

NAC was administered postoperatively to 44 of the 92 patients with preoperative CKD in order to diminish renal injury and subsequent ARF but the obtained results showed insignificant benefits in preventing eGFR reduction, need for hemodialysis or postoperative complications of ICU admission. These results are consistent with the ones obtained by other studies no matter the dose, timing and way of administration [15-18].

The inefficiency of NAC administration could be due to the different mechanism of ARF in cardiac surgery compared to nephrotoxic drug administration or other conditions [19]. Variances in renal perfusion pressures during CBP and in ICU could be the factors responsible of postoperative ARF in patients with CKD. Adequate volemic and hemodynamic control might prove efficient in preventing ARF but more extensive studies are subsequently needed in order to attest the veridicality of the theory [18].

Post-cardiac surgery ARF is common and associated with a significant increase in morbidity and mortality. 15.21% of our CKD group needed dialysis in the early postoperative phase independent to NAC administration. Unfortunately, data found in literature regarding the prevention and management of postoperative ARF is scarce and controversial. Several agents have been tested but no pharmacological intervention significantly proved to reduce mortality. In a recent meta-analysis, dopamine caused a significant reduction in creatinine clearance; fenoldopam, atrial natriuretic peptide and brain natriuretic peptide show evidence of renoprotection [20]. Another published review found that fenoldopam and angiotensin-converting enzyme inhibitors were associated with a reduction in ARF, whereas other vasodilator agents were noted to have no effect on the incidence of ARF. From the natriuretic and/or diuretic cohort, only atrial natriuretic peptide and B-natriuretic peptide were associated with a reduction in ARF, whereas the remaining agents from this group were noted to have no effect on the incidence of ARF. Amongst the other interventions that were reviewed, the off-pump surgical technique and pulsatile flow techniques were associated with a reduction in the incidence of ARF, whereas interventions such as clonidine, albumin infusion, isotonic saline infusion, and insulin therapy were not associated with a reduction in postoperative ARF [21]. Randomized studies evaluating the effect of novel renoprotective agents that are powered to detect clinically relevant differences in outcomes are required.

The current study is limited by the small number of patients with CKD and the absence of preoperative exclusion criteria (like iodinated contrast administration and nephrotoxic medical usage in the days preceding surgery).

Conclusions

Despite induction of glutathione synthesis, vasodilatory and antioxidant properties, the results of the current study suggest that NAC administration in patients with CKD brings little to no benefit in the prevention of postoperative ARF. Based on these results, our future research will involve different compounds with better outcome.

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