Assessment of Renal and Hepatic Tissue-Protective Effects of N-Acetylcysteine via Ammonia Metabolism: A Prospective Randomized Study

Authors' Contribution:
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Background: The present study sought to assess the renal and liver protective effect of N-acetylcysteine through NH3 and urea metabolism in patients with chronic obstructive pulmonary disease who were scheduled for coronary artery bypass grafting surgery.

Material/Methods: Patients with chronic obstructive pulmonary disease (COPD) who were scheduled for coronary artery bypass grafting were divided into 2 groups so as to receive (Group 1, n=35) or not receive (Group 2, n=35) 900 mg/day of n-acetylcysteine for 7 days before the operation starting from their admission to the service by a pulmonologist with the purpose of treating COPD until the day of surgery. Both groups were subjected to the same anesthesia protocol. Blood samples were taken preoperatively, within the first 15th minute following cessation of the cardiopulmonary bypass, at postoperative 24th hour, and at postoperative 48th hour. Blood tests included ammonia (NH3), lactate, blood urea nitrogen, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), troponin I (Tn I), and creatinine kinase-muscle brain (CKMB).

Results: There was a significant difference between the groups' NH3 and lactate levels after cardiopulmonary bypass, postoperative 24th hour, and postoperative 48th hour (respectively, NH3: 39.0±8.8 *vs.* 55.4±19.6 and 40.1±8.4 *vs.* 53.2±20.2 mcg/dl, lactate: 1.7±0.9 *vs.* 2.1±1.2 and 1.2±0.5 *vs.* 1.8±1.4 mmol/L; p<0.01). Creatinine and BUN levels in Group 2 were found to be significantly higher at the postoperative 48th hour compared to the levels of Group 1 (P<0.05).

Conclusions: N-acetylcysteine pretreatment appears to improve renal and hepatic functions through regulation of ammonia and nitrogen metabolism and reduction of lactate in patients with chronic obstructive pulmonary disease who undergo coronary artery bypass grafting surgery. We found that N-acetylcysteine improved kidney and/or liver functions.

MeSH Keywords: **Acetylcysteine • Coronary Artery Bypass • Pulmonary Disease, Chronic Obstructive**

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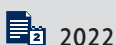
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Background

Chronic obstructive pulmonary disease (COPD) is among the leading causes of death worldwide, with an estimated prevalence of 9% to 10% in the general population [1]. However, COPD was reported to be far more prevalent among patients scheduled for coronary artery bypass grafting (CABG) and it has also been suggested that declined respiratory function is the main predictor of mortality in patients undergoing CABG [2,3].

Postoperative organ failure is an important predictor for early mortality in patients undergoing on-pump coronary artery bypass grafting [4]. Activation of the inflammatory cascade during extracorporeal circulation and development of ischemia-reperfusion injury are known to be responsible for failure of various organ and systems including pulmonary, liver and renal dysfunction [5]. Patients with COPD more tend to have several comorbidities after CABG since these patients already have several comorbidities before the operation [6]. It was also demonstrated that COPD severity is correlated with the postoperative occurrence risk of occurrence of severe organ and system dysfunction [7].

Recently, there has been a trend towards the protection of organs against deleterious effects of the cardiopulmonary bypass that occurs during cardiac surgery [8]. N-acetylcysteine, which has long been used as the antidote to acetaminophen, has become used due to its presumed protection against ischemia-reperfusion injury in tissues [9]. Based on its free radical scavenger properties and maintenance of cellular glutathione status, its use has increasingly become generalized in many areas, with varying evidence. Although studies failed to demonstrate renal protective effect of perioperative use of N-acetylcysteine, its use was demonstrated to preserve pulmonary functions in patients undergoing CABG [10,11]. The present study sought to investigate the potential renal and hepatic protective effect of n-acetylcysteine through NH3 and urea metabolism in patients with chronic obstructive pulmonary disease undergoing coronary artery bypass grafting surgery.

Material and Methods

The Institutional Ethics Board of Erzincan University approved the study (ID; 44495147-181). This prospective, randomized study included 70 patients who had been diagnosed with COPD at a chest diseases clinic, had a FEV1 (volume taken at the first second of forced expiration) of 50% to 80%, and who were scheduled for CABG. The diagnosis of COPD was confirmed by reviewing the patients' counseling charts, radiography reports, and spirometer testing results archived by the Department of Chest Disease. Patients with a history of renal or hepatic failure and those with abnormal findings in kidney

or liver functional parameters, as well as in the tests showing liver cell and cholestatic damage in the preoperative laboratory assessment, were excluded from the study. Patients were divided into 2 groups to receive (Group 1, n=35) or not receive (Group 2, n=35) 900 mg/day of n-acetylcysteine for 7 days until the day of surgery. Both groups were subjected to the same anesthesia protocol. Blood samples were taken preoperatively, within the first 15th minute following cessation of the cardiopulmonary bypass, at postoperative 24th hour, and at postoperative 48th hour. Blood tests included ammonia (NH3), lactate, blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), troponin I (TnI), and creatinine kinase-muscle brain (CKMB).

Serum levels of BUN, AST, ALT, ALP, and CKMB were measured using an Olympus AU2700TM Chemistry ImmunoAnalyser Device (Tokyo - JAPAN). Lactate levels were measured with Beckman Coulter lactate reagent (Beckman Coulter, Inc., USA) using an Olympus AU2700TM Chemistry ImmunoAnalyser Device in plasma samples obtained with sodium fluoride/potassium oxalate tubes. Serum TnI levels of the patients were measured with a Siemens Advia Centaur XP immunoassay device (Deerfield, IL, USA). Serum NH3 levels were measured with infinity ammonia reagent (ThermoFisher Scientific-Middletown, USA) using an Olympus AU400 Chemistry Analyzer device (Tokyo, JAPAN) in plasma samples obtained with EDTA-containing tubes.

Statistical analyses

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 20.0. Descriptive statistics are reported as mean ± standard deviation for continuous variables and as frequency and percentage for categorical variables. Parameters with a normal distribution were compared using the unpaired t test, whereas parameters not demonstrating normal distribution were compared using the Mann-Whitney test. A p value of less than 0.05 was considered as statistically significant.

Results

Comparison of baseline characteristics between the 2 groups is demonstrated in Table 1. No significant difference was found between the 2 groups in terms of age (43±15 *vs.* 41±17 years, p>0.05), body mass index (BMI) (27±3.2 *vs.* 27±3.0, p>0.05), waist circumference (91±9 *vs.* 94±8 cm, p>0.05), tobacco or alcohol use, and laboratory findings (p>0.05). Also, there was no significant difference between the groups regarding the seriousness of COPD (FEV1) (P>0.005) (Table 1).

Serum AST, ALT, ALP, CK-MB, and TnI levels demonstrated no significant difference between the 2 groups at any of the 4

Table 1. Patient characteristics and analysis results grouped to according to received N-acetylcysteine treatment.

	All patients	NAC in treat	No treat	P values*
N	70	35	35	–
Male, (%)	40 (57)	20 (57)	20 (57)	–
Female, (%)	15 (43)	15 (43)	15 (43)	–
Age, year	42±16	43±15	41±17	[a]0.6715
BMI, kg/m²	26.9±3.1	27.1±3.2	26.6±3.0	[a]0.4437
WC, cm	93±9	91±9	94±8	[a]0.1536
Cigarette use, (%)	25 (36)	12 (34)	13 (37)	[b]0.8383
Alcohol use, (%)	17 (24)	7 (20)	10 (29)	[b]0.5293
Glucose, mg/dl	98±16	99±15	98±17	[a]0.7719
Leukocyte, 10³/ul	7.6±1.3	7.5±1.4	7.7±1.2	[a]0.5326
Hematocrit,%	43,4±5.8	43.7±5.3	43.0±6.4	[a]0.6049
Grade of COPD (FEV1)	66.1±7.7	66.9±7.8	65.3±7.5	[a]0.3874

* Comparison between NAC in treat and no treat. a Unpaired t test; b Mann-Whitney Test, BMI – Body mass index; WC – waist circumference; COPD – chronic obstructive pulmonary disease; FEV1 – volume taken at the first second of forced expiration. Glucose, Leukocyte, and hematocrit values belong to the preoperative period.

measurement time points (preoperative, during cardiopulmonary bypass, 24th postoperative hour, and 48th postoperative hour) ($p > 0.05$) (Table 2). Serum NH3 levels of the 2 groups were also similar in the preoperative period (37.4±9.09 *vs.* 41.4±11.46 mcg/dl for Group 1 and 2, respectively, unpaired *t* test $p > 0.05$) whereas the differences in NH3 levels were significant after cardiopulmonary bypass (37.8±10.26 *vs.* 47.0±14.57, for Group 1 and 2, respectively, $p < 0.05$, unpaired *t* test), at 24th hour (39.0±8.80 *vs.* 55.4±19.64, for Group 1 and 2, respectively, $p < 0.05$, unpaired *t* test) and at 48th hour (40.1±8.44 *vs.* 53.2±20.15, for Group 1 and 2, respectively, $p < 0.05$, unpaired *t* test) (Figure 1). Serum BUN levels demonstrated no significant difference in the preoperative period (17.6±4.99 *vs.* 18.6±4.72, for Group 1 and 2, respectively, $p > 0.05$) and after cardiopulmonary bypass (17.1±4.61 *vs.* 19.6±8.56, for Group 1 and 2, respectively, $p > 0.05$) whereas the differences were significant at 24th postoperative hour (18.7±4.36 *vs.* 24.4±9.52, for Group 1 and 2, respectively, $p < 0.05$) and 48th postoperative hour (19.8±5.42 *vs.* 24.9±10.90, for Group 1 and 2, respectively, $p < 0.05$) (Figure 2). Lactate levels at 24th and 48th postoperative hours were significantly higher in Group 1 when compared to Group 2 ($p < 0.05$) (Figure 3). Creatinine levels at the 48th postoperative hour were significantly higher in Group 2 when compared to Group 1 ($p < 0.05$).

Discussion

There have been several studies demonstrating the beneficial effects of N-acetylcysteine on renal and hepatic functions [12–16].

N-acetylcysteine has begun to be used in a wide variety of clinical settings, including management of chronic periodontitis, treatment of acute pulmonary damage, palliation of peripheral neurotoxicity, to provide myocardial protection during extracorporeal circulation, and to prevent atrial fibrillation after CABG [17–20]. NAC has been reported to be beneficial due to its anti-oxidant and central anti-inflammatory properties. Moreover, past studies have proved that NAC, which is described with similar mechanisms in experimental animals, is useful in both non-acetaminophen- and non-acetaminophen-induced acute liver diseases [21,22]. However, high costs still prevent fully explaining the effects of NAC use in COPD patients who are recommended for integrated care [23].

A gradual increase in blood NH3 levels was found to be associated with cerebral edema, coma, and progressive decline in intellectual functions, while severe hyperammonemia may result in irreversible neurotoxicity and cellular necrosis in the central nervous system. Since glucose is the main source of energy that is utilized by the neurons of the central nervous system, the brain tissue cannot adapt quickly to use alternative energy compounds, such as free fatty acids, when the supply of the glucose to the neurons decreased. This is due to the fact that free fatty acids cannot pass through the blood-brain barrier. However, in situations where glucose supply to the central nervous system declines rapidly, brain tissue may utilize ketone bodies (e.g., hydroxybutyrate and acetoacetic acid) derived from fatty acid metabolism. One of the major causes of hyperammonium toxicity in the brain is that it inhibits the continuation of the TCA cycle and energy production by causing
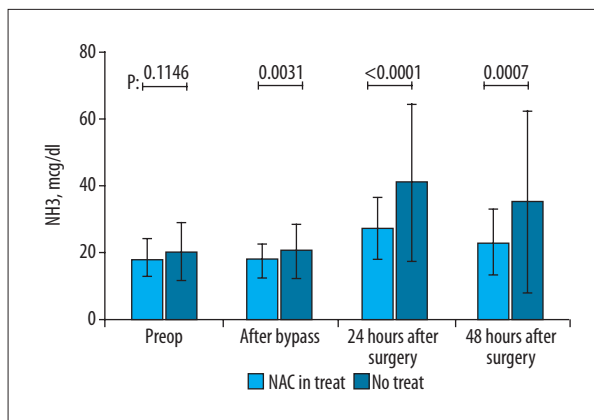
Table 2. Comparison of study parameters between two groups. Blood samples were taken at four different time points.

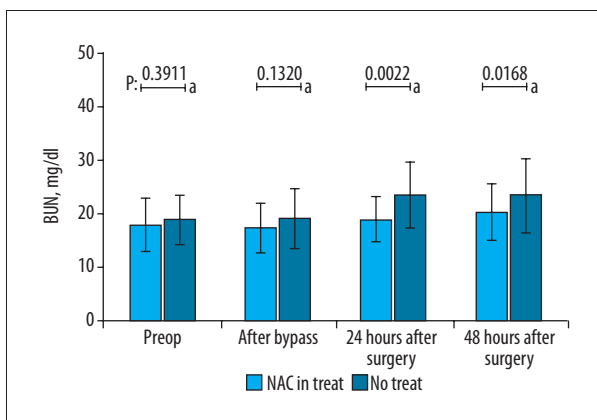| Variable	All patients n=70	Group 1 (N-acetylcysteine) n=35	Group 2 (Controls) n=35	P values*
Creatinin, mg/dl				
Preop	0.97±0.23	0.94±0.20	1.01±0.26	[a]0.2412
After bypass	1.00±0.24	1.00±0.23	0.99±0.25	[a]0.8598
At the 24th hour after surgery	1.11±0.29	1.09±0.24	1.13±0.33	[a]0.5708
At the 48th hour after surgery	1.17±0,32	1.08±0.31	1.25±0,30	[a]0.0237
BUN, mg/dl				
Preop	18±4.9	18±5.0	18±4.6	[a]0.4479
After bypass	18±7.0	17±4.6	19±5.7	[a]0.2019
At the 24th hour after surgery	22±8.0	19±4.4	23±6.2	[a]0.0010
At the 48th hour after surgery	22±9.0	20±5.4	23±6.9	[a]0.0287
AST, IU/L				
Preop	25±12	26±13	23±10	[a]0.3360
After bypass	35±20	36±16	34±23	[a]0.5599
At the 24th hour after surgery	45±31	41±17	48±41	[b]0.8555
At the 48th hour after surgery	48±35	42±22	55±44	[a]0.1297
ALT, IU/L				
Preop	24±14	24±16	25±11	[a]0.9520
After bypass	26±17	25±18	28±16	[b]0.1923
At the 24th hour after surgery	32±23	30±23	33±23	[b]0.3384
At the 48th hour after surgery	29±20	30±25	29±15	[b]0. 6217
ALP, IU/L				
Preop	78±28	75±31	82±24	[a]0.3525
After bypass	72±23	69±26	75±19	[a]0.2440
At the 24th hour after surgery	78±29	78±35	78±23	[a]0.9612
At the 48th hour after surgery	71±25	69±20	74±29	[a]0.3422
CK-MB, IU/L				
Preop	17±8	18±8	17±8	[b]0.6510
After bypass	37±28	37±24	36±32	[a]0.8774
At the 24th hour after surgery	53±61	52±28	54±82	[b]0.0954
At the 48th hour after surgery	40±56	32±19	48±77	[b]0.2131
TnI, ng/ml				
Preop	0.33±0.91	0.38±1.20	0.28±0.47	[b]0.4557
After bypass	3.76±7.09	3.58±5.15	3.93±8.68	[b]0.6427
At the 24th hour after surgery	6.85±9.43	5.05±5.80	8.64±11.84	[b]0.6724
At the 48th hour after surgery	8.87±10.90	7.15±7.06	10.59±13.61	[a]0.1887
NH3, mcg/dl				
Preop	39.4±10.5	37.4±9.1	41.4±11.5	[a]0.1146
After bypass	42.4±13.3	37.8±10.3	47.0±14.5	[a]0.0031
At the 24th hour after surgery	47.2±17.2	39.0±8.8	55.4±19.6	[a]<0.0001
At the 48th hour after surgery	46.6±16.7	40.1±8.4	53.2±20.2	[a]0.0007
Lactate, mmol/L				
Preop	1.0±0.4	0.9±0.3	1.0±0.4	[a]0.2655
After bypass	1.0±0.3	0.9±0.3	1.0±0.4	[a]0.0828
At the 24th hour after surgery	1.7±0.9	1.4±0.5	2.1±1.2	[a]0.0018
At the 48th hour after surgery	1.5±1.1	1.2±0.5	1.8±1.4	[b]0.0083

* Comparison was based on [a] unpaired t test; [b] Mann-Whitney Test.
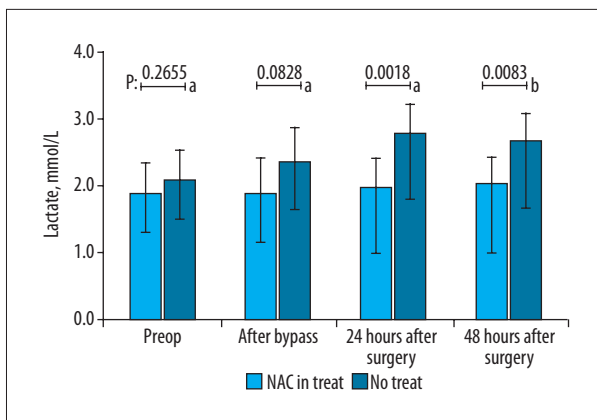
Figure 1. Comparison of the serum NH3 levels between groups with regard to samples taken at preoperative period, after cardiopulmonary bypass, at 24th postoperative hour, and at 48th postoperative hour. NH3 levels demonstrated no difference preoperatively whereas patients in N-acetylcysteine group had significantly lower NH3 levels in all other measurement time points (p<0.05, unpaired *t* test).

Figure 2. Comparison of BUN levels at 4 consecutive time points. No significant difference was found in the preoperative period and after cessation of cardiopulmonary bypass, whereas patients in N-acetylcysteine group had significantly lower BUN levels at the 24th and 48th postoperative hours (p<0.05, unpaired *t* test).

the consumption of the vital enzyme of the cycle, α-ketoglutarate. In addition, hyperammonemia reduces the glutamate transporter molecules by inducing the receptors of N-metil-D-aspartate (NMDA) and GABA, which results in an increase in the intracellular amount of GABA and glutamine. These changes alter cellular membrane permeability and increase intracranial pressure, leading to brain edema [24–27]. In our study, we found that N-acetylcysteine pretreatment was associated with a significant decrease in serum NH3 levels immediately after the cessation of cardiopulmonary bypass, and this decline was sustained up to the 48th postoperative hour. These findings

Figure 3. Comparison of serum lactate levels at four consecutive time points. No significant difference was found in the preoperative period and after cessation of cardiopulmonary bypass, whereas patients in N-acetylcysteine group had significantly lower lactate levels at the 24th and 48th postoperative hours (p<0.05, unpaired *t* test).

suggest the preventive effect of N-acetylcysteine against the toxic effects of hyperammonemia after CABG.

Our finding that lactate levels were significantly lower in patients receiving N-acetylcysteine pretreatment may be attributed to increased microcirculation and oxygenation in liver and other tissues [28–31]. We also found that serum BUN levels at the 24th and 48th postoperative hours were significantly lower in patients receiving N-acetylcysteine when compared to controls, as evidence of the positive effects of N-acetylcysteine on renal functions. The lower creatinine levels we found at the 48th hour in patients who received N-acetylcysteine pretreatment compared to controls may support this finding. Renal protective mechanisms of N-acetylcysteine are likely to be same as those for liver tissue.

There have been several studies evaluating the tissue- and organ-protective effects of n-acetylcysteine in patients undergoing cardiac surgery on extracorporeal circulation. In one study, Fisher et al. [32] found that N-acetylcysteine treatment caused a significant decrease in serum creatinine in patients undergoing cardiac surgery. Sucu et al. [33] demonstrated that intravenous administration of N-acetylcysteine alleviated the pump-induced oxido-inflammatory response that developed during extracorporeal circulation. Şavluk et al. [13] demonstrated that intravenous N-acetylcysteine prophylaxis was associated with an improvement in renal functional tests in patients with moderate renal failure. These findings are in line with ours to some extent.

We observed no difference between the groups with regard to smoking status and alcohol use, supporting that the difference

in serum lactate and NH3 levels we found between groups could essentially be attributed to the effect of N-acetylcysteine.

In clinical practice, both cytosolic and mitochondrial enzyme AST and cytosolic enzyme ALT are aminotransferases that are used to evaluate hepatocellular damage. ALP, synthesized in bile duct epithelial cells, is a test used to evaluate cholestatic damage. ALT is relatively more specific to the liver. Aminotransferases are sensitive markers in liver diseases that accompany hepatic cell damage such as hepatitis [34]. The increase in serum aminotransferase level is associated with the passing of the in-cell enzyme to the serum due to hepatocellular necrosis. Briefly, ALT and AST are not the fundamental liver function tests. It has been reported that the hepatic metabolism of lactate is about 100 mmol per hour, and that this value can fall by 0.6 mmol/kg per hour if the patient has acute renal insufficiency [35]. Therefore, approximately 70% of the blood lactate clearance is performed by the liver, while the kidneys contribute by renal excretion. In this study, lactate levels were low due to the positive effect of N-acetyl cysteine on liver and kidney functions. However, no significant difference was found between the 2 groups in liver-associated aminotransferases. This is probably due to the fact that aminotransferases are the indicators of extreme cell damage that is caused by liver function. The lower incidence of ammonia in the same patient group was associated with the positive effect of ammonia metabolism, which is one of the major functions of the liver. This result also explains the decrease in lactate levels.

Another important finding of the present study is that use of blood urea levels seem to be more appropriate than using creatinine levels for early detection of the renal protective effects of N-acetylcysteine. This finding indicates that the actual protective effect of the N-acetylcysteine is caused by NH3 and urea metabolism. Supporting these, several studies suggested that blood creatinine levels might be misleading in early detection of renal impairment after cardiac surgery, and creatinine levels may even be as increased when renal functions are severely impaired [36–38].

The limitations of this study are the small number of patients and the exclusion of patients with abnormalities in liver and renal function tests.

Conclusions

In conclusion, our study demonstrated that N-acetylcysteine pretreatment has a stabilizing effect on NH3 and nitrogen metabolism in COPD patients undergoing CABG. Patients with COPD who were started on N-acetylcysteine before surgery tend to have lower lactic acid levels, indicating a protective effect of N-acetylcysteine against renal and hepatic tissue damage.

Conflict of interest

None.

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