Effect of N-acetylcysteine on microalbuminuria in patients with acute respiratory distress syndrome

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Abstract

Introduction: Acute respiratory distress syndrome (ARDS) is associated with enlarged permeability of respiratory capillaries resulting in interstitial edema and microalbuminuria. This study investigated the effect of early treatment with N-acetylcysteine (NAC) on microalbuminuria/creatinine ratio and clinical improvement in ARDS.

Material and methods: Twenty-three patients with ARDS were randomly entered into two groups of study including regular therapy and regular therapy plus NAC. NAC was started with 150 mg/kg on the first day followed by 50 mg/kg at the second day. Urine sample was tested for microalbuminuria on 4, 6, 12, 24, 36, and 48 h post baseline.

Results: No significant correlation was found between microalbumin/creatinine ratio (MACR) and acute physiology and chronic health evaluation (APACHE II) or PaO_2/FiO_2 ratio and blood pressure in each group. Non-survivors showed higher urine albumin creatinine ratio (ACR) and physiologic scores than survivors. The patients outcome who treated with NAC showed significant improvement comparing with controls.

Conclusions: NAC improves global hypoxemia in the patients with acute lung injury. Improvement of oxidant/antioxidant balance by NAC increases the survival of patients with ARDS who are under oxidative crisis. Although limitations of this study do not let us to reach a conclusive decision but the impact of microalbominuria as a predictive of survival in ARDS patients receiving NAC seems essential. Conducting larger clinical trials are recommended.

Key words: N-acetylcysteine, acute respiratory distress syndrome, microalbuminuria.

Introduction

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are almost similar diseases occurring in respiratory tract. ARDS is a syndrome of severe dyspnea with rapid onset of edema and hypoxemia whereas ALI appears by inflammation and increased permeability with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension. The distinction between ALI and ARDS is the degree

of hypoxemia. ALI is defined by a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio of less than 300 mm Hg while 200 mm Hg or less is required for ARDS. Approximately 10% of patients who admit to intensive care unit (ICU) suffer from acute respiratory failure, whom 20% are diagnosed as acute lung injury (ALI) or ARDS [1, 2]. Despite advances in supportive care, the mortality rate of the patients with ARDS remains high [3, 4].

Activation of pulmonary endothelium and macrophages leads to release of cytokines and accumulation of neutrophils inside the pulmonary microvasculature [5, 6]. Simultaneously, proteolytic enzymes, reactive oxygen species (ROS), and additional inflammatory cytokines are released [7-9]. In ARDS, there is extensive overproduction of free radicals to the extent that endogenous anti-oxidants are overwhelmed. N-acetylcysteine (NAC) is a thiol-containing compound acting as a precursor of glutathione. The benefit of NAC in the management of ARDS has been proved by measuring patient's intracellular glutathione (inside red blood cells) and extracellular (plasma) anti-oxidant defense biomarkers and outcome. It has been shown that treatment by NAC increases extracellular total anti-oxidant power and total thiol molecules and improves intracellular glutathione and the outcome of the patients [10]. Recent animal study also confirmed antioxidant potential of NAC [11].

The hypothesis of the present work is that administration of NAC improves outcome of ARDS patients.

Material and methods

Subjects

After obtaining approval from ethics committee of TUMS and written informed consent from relatives, on the basis of inclusion criteria 23 patients were randomly entered into the study. The study was conducted in the ICU of a University Hospital from September 2006 to September 2007. The patients were included if they required mechanical ventilation and had a PaO_2/FiO_2 of lower than 200 mm Hg and pulmonary capillary wedge pressure (PCWP) of lower than 18 mm Hg.

Exclusion criteria were: PaO_2/FiO_2 > 200 mm Hg, left ventricular failure defined echocardiographically as the concomitant presence of an increased left ventricular end diastolic diameter (> 60 mm) and volume (> 120 cm^3), the presence of regional and global left ventricular hypokinesia and a left ventricular fractional area contraction of < 4 under inotropic support, chronic respiratory failure (chronic hypoxemia, hypercapnia, severe asthma), chronic renal failure (creatinine level > 2 mg/dl or renal replacement therapy), known allergy to NAC, diabetes mellitus, age less than 18-years old, pregnancy, and any medical condition considered to be irreversible or lethal within 48 h after ICU admission. The etiologies of ARDS in study patients were multiple trauma (7 cases), sepsis (3), peritonitis (4), pneumonia (4), and uncertain (5 cases).

Treatment protocol

NAC was purchased from UCB Pharma ltd (UK). Among the included patients, 9 received NAC (150 mg/kg) diluted in 5% dextrose and infused in a period of 20 min at first and continued by 50 mg/kg/day diluted in 5% dextrose (50 ml) on the second day. Fourteen patients in the control group underwent standard treatment without NAC.

All patients had radial and pulmonary artery catheters. If necessary, patients received mechanical ventilation under continuous sedation with midazolam and fentanyl. Crystaloids were infused to obtain a central venous pressure between 8-12 mm Hg. If the cardiac index remained > 2.5 l/min/m^2, dobutamine was administered at a value between 3 and 3.5 l/min/m^2. Norepinephrine was added to maintain mean arterial pressure > 60 mm Hg.

Clinical proteinuria was defined by albumin creatinine ratio (ACR > 300 mg/day). This corresponds to daily albumin excretion of > 300 mg/day. ACR values between 30 and 299 mg/g were considered normal.

Fresh urine samples were collected from patients via a urinary catheter before infusion of NAC and 4, 6, 12, 24, 36, 48 h after that and kept frozen at –20°C until analysis. Urine albumin concentration was measured by immunoassay turbidimetric using Technicon RA-XT 1000 analyzer. To exclude the influence of intraindividual variation in urinary flow rate, microalbumin was estimated per creatinine and reported as microalbumin/creatinine ratio (MACR). The assigned laboratory reference range was < 2.3 mg/mmol.

Acute physiology and chronic health evaluation (APACHE II)

The APACHE II scoring method was used to predict risk of ICU mortality. The APACHE II score was measured on a daily basis for all patients admitted to ICU. The point score was calculated from 12 routine physiological measurements during the time of study. For calculating APACHE II score, arterial blood gases, electrolytes, and complete blood counts were determined daily, and blood pressure, heart rate, respiratory rate, body temperature, pulmonary indices, and hemodynamic profiles were checked and recorded and mean daily values were calculated [10]. Information about previous health status, age and sex, surgical status (elective or emergency surgery), and major reason for ICU admission and severity of illness (acute physiologic state) were included.

Table I. Demographic data of patients on the day of admission

Parameter	Control	NAC	*p* Value
Age	45.57 ±18.275	50.56 ±22.27	0.560
Male/female	9/5	6/3	0.863
MACR	21.48 ±23.79	22.42 ±18.46	0.890
APACHE II	20 ±5.7	21.8 ±4.48	0.360
PaO_2	95.150 ±24.6	105.380 ±31	0.395
FiO_2	58	53	0.161
PaO_2/FiO_2	183.73 ±58.93	195.67 ±38.50	0.659
MAP [mm Hg]	87.64 ±11.84	97.11 ±16.18	0.122
GCS	9.35 ±4.16	10.33 ±6.94	0.631
Temperature	37.5 ±1.07	37.17 ±1.28	0.549
HR [/min]	103.6 ±23.22	108.33 ±13.15	0.671
RR [/min]	13.7 ±13.49	17 ±14.29	0.451
WBC	14.32 ±6.8	14.02 ±7.59	0.875

Data are mean ± SD
MACR – microalbumin creatinine ratio, APACHE – Acute Physiology and Chronic Health Evaluation, MAP – mean arterial pressure, GCS – Glascow Coma Scale, HR – heart rate, RR – respiratory rate, WBC – white blood cells

Statistical analysis

Data are shown as means ± SE. Mann-Whitney U test was used for analysis of nonparametric data. A *p*-value of less than 0.05 was considered statistically significant. The relationship between MACR and survival was explored using multiple logistic regression. Spearman rank correlation coefficients (*r*) was used to quantify the correlation between variables.

Results

A total of 23 patients with the age range of 21-72 and mean age of 48 years were enrolled in study. Clinical characteristics of the patients are summarized in Table I. Nine patients were treated with NAC and 14 without NAC as control group. No adverse effect was recognized by NAC. The etiologies of ARDS in study patients were multiple trauma (7 cases), sepsis (3), peritonitis (4), pneumonia (4), and uncertain (5). Age and gender were not differed between treatment groups. Patients in both groups' required mechanical ventilation and intensive care for similar period.

MACR during the study: Median MACR for patients in NAC group was decreased after 4 h and remained low. In the control group, mean MACR remained increased for 48 h. Although, MACR in NAC group showed a decreasing trend but the difference with the control was not statistically significant (Figure 1). The *p* values of changes between two groups at times 0, 4, 6, 12, 24, 36, 48 were 0.56, 0.89, 0.64, 0.93, 0.08, 0.23, and 0.06, respectively

MACR and survival: Median MACR for survived patients was less than those who did not survive but the difference was not statistically significant ($p = 0.073$, Figure 2).

MACR and PaO_2/FiO_2 ratio: An improvement in PaO_2 was seen with increase of MACR but no statistically significant correlation was found between MACR and PaO_2/FiO_2 in control ($p = 0.779$) or NAC ($p = 0.441$) groups (Figure 3).

MACR and APACHE II score: The correlation between MACR levels and APACHE II score was not statistically significant in NAC ($p = 0.414$) or control ($p = 0.779$) groups (Figure 4).

MACR and mean arterial pressure (MAP): Comparison of correlation between MACR and MAP showed no significant difference in NAC ($p = 0.478$) or control ($p = 0.279$) groups (Figure 5). Most of study patients were normotensive but in 6 patients who were hypertensive (BP > 140/90),

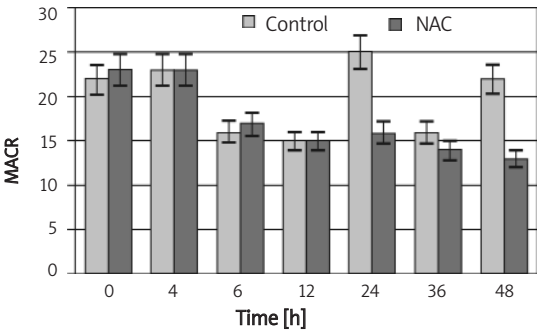


Figure 1. Microalbumin creatinine ratio (MACR) during the study
MACR in the NAC group shows a decreasing trend but the difference with the control is not statistically significant. The *p* values of changes between two groups at times 0, 4, 6, 12, 24, 36, and 48 h are 0.56, 0.89, 0.64, 0.93, 0.08, 0.23, and 0.06, respectively.

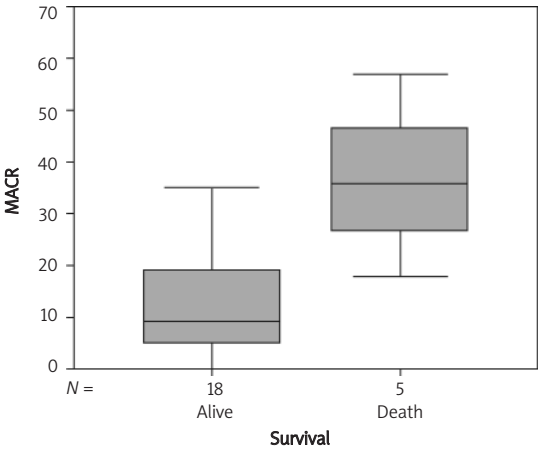


Figure 2. Correlation between microalbumin creatinine ratio (MACR) and survival
Mean MACR for survived patients is less than those who did not survive but the difference was is statistically significant ($p = 0.073$).

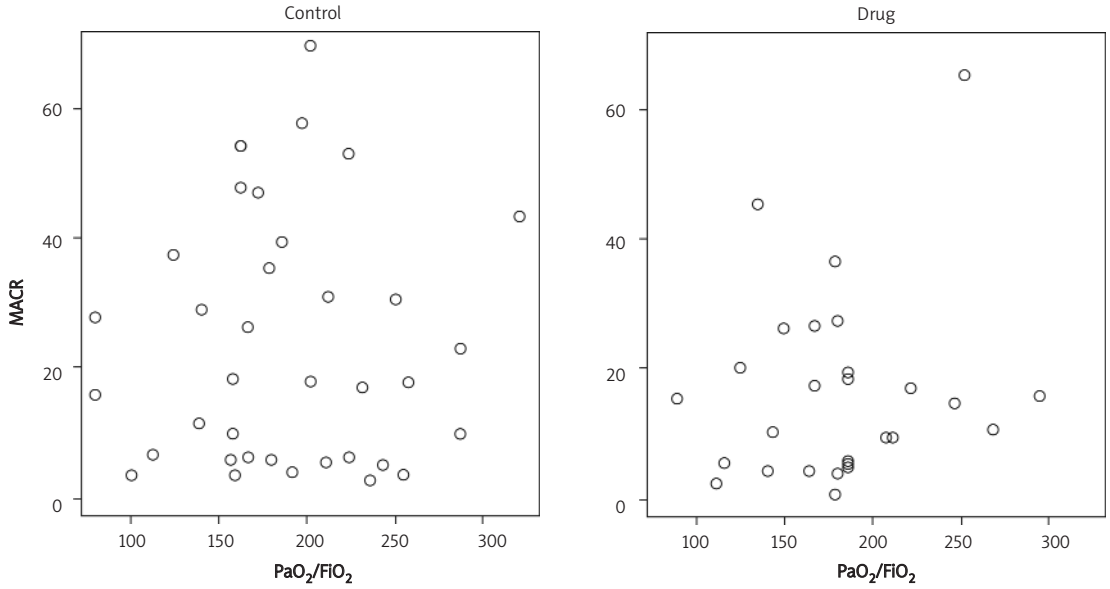
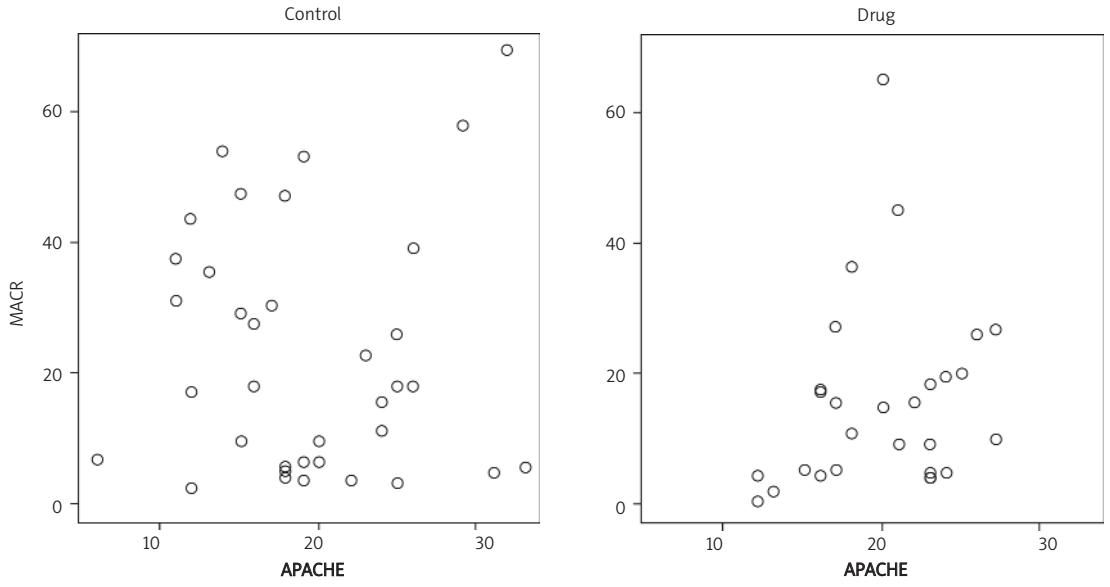


Figure 3. Correlation between microalbumin creatinine ratio (MACR) and PaO_2/FiO_2 during study
There is no statistically significant correlation between MACR and PaO_2/FiO_2 in control (p = 0.779) or NAC (p = 0.441) groups.



APACHE – Acute Physiologic and Chronic Health Evaluation

Figure 4. Correlation between microalbumin creatinine ratio (MACR) and APACHE during study
The correlation between MACR and APACHE score is not statistically significant in NAC (p = 0.414) or control (p = 0.779) groups.

MACR was increased with augmentation of arterial pressure.

No statistically significant change was observed within or between groups when examined at different time points. Perfusion pressure and cardiac index were well maintained throughout the study in both treatment groups.

Patient's outcome: According to APACHE II, a significant improvement in outcome of patients was observed in patients who were treated by NAC (p = 0.04, Figure 6).

Discussion

Usually, every intervention that could suppress neutrophils or improve antioxidant potential status in conditions characterized by oxidative stress such as ARDS or sepsis can be beneficial [2, 12]. In these conditions, early and accurate identification of patients with high risk of death allows for aggressive therapeutic interventions. Administration of NAC during the first hours of severe sepsis and septic shock has decreased peroxidative stress, enhanced

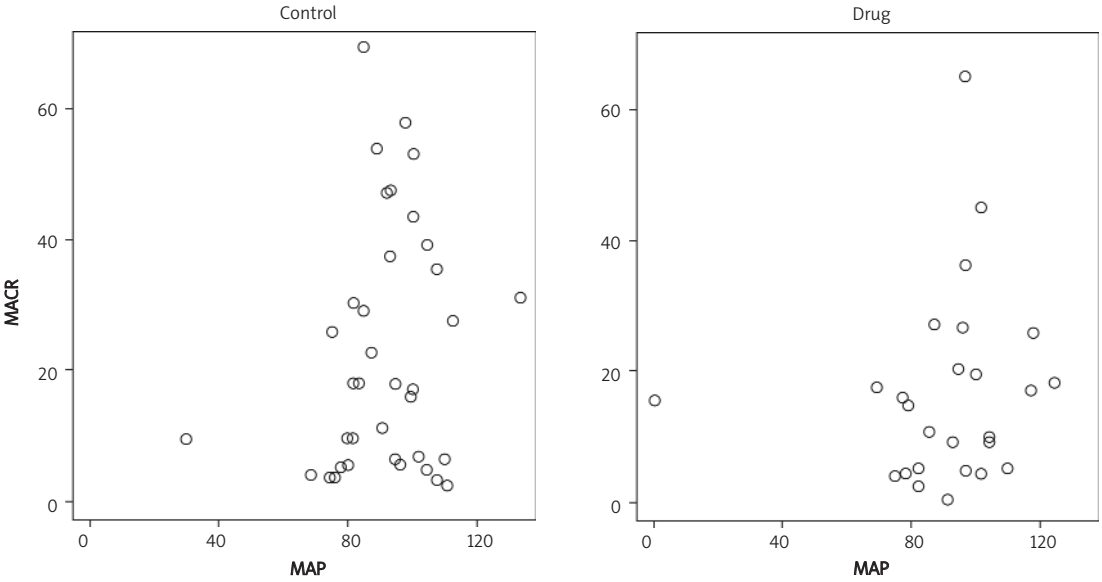
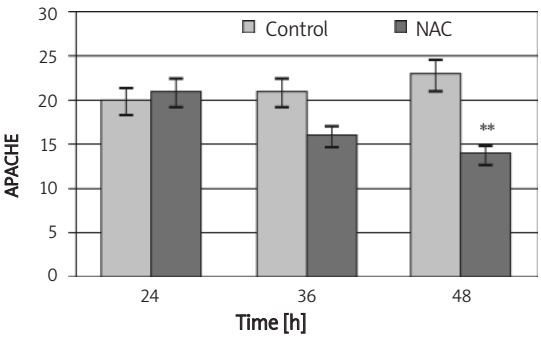


Figure 5. Correlation between microalbumin creatinine ratio (MACR) and mean arterial pressure (MAP)
Comparison of correlation between MACR and MAP showed no significant difference in NAC (p = 0.478) or control (p = 0.279) groups.

tissue oxygenation [14], and improved respiratory function [14]. There is evidence that NAC acts as an anticoagulant and perhaps decreases pulmonary fibrin uptake during ARDS [15]. On the other hand, another small trial with NAC did not show significant improvement on systemic oxygenation or the need for ventilatory support [16]. In addition, delayed administration of NAC not only failed to improve tissue oxygenation but also adversely affected survival in critically ill patients with established organ failure [17]. In fact, endothelial damage cannot be measured directly, thus, MACR seems to be a valuable substitute [18] especially because of speed and consistency of the microvascular response to acute injury [19]. Measurement of microalbuminuria during first 6 h after admission provides precious information about outcome of patients with ARDS and their organ failure [20]. It has been shown that micro-albuminuria reaches its peak levels 2 days faster than other inflammatory biomarkers [21] and thus can be used to predict occurrence of ARDS following trauma [18].



APACHE – Acute Physiologic and Chronic Health Evaluation

Figure 6. APACHE score during the study in two groups
The p value for changes between two groups at times 24, 36, and 48 is 0.37, 0.16, and 0.04, respectively (**p = 0.04).

In the present study, we were unable to find a relationship between MACR and APACHE II that is in contrary to other studies [20, 22] but in agreement with another [23]. Our findings also remain in agreement with another study showing absence of correlation between MACR and extravascular lung water, a possible indicator of vascular permeability in septic patients receiving mechanical ventilation [24]. The present study showed that non-survivors had higher urine ACR and physiologic scores as compared to survivors. Thus, capillary permeability assessed as microalbuminuria could predict survival or death and probabilities derived from illness severity scoring system. Our study didn't show a significant correlation between MACR and PaO_2/FiO_2 which is supported by other reports [23, 24]. Furthermore we were unable to find correlation between diastolic, systolic or MAP and albumin excretion rate, which is supported by one study [25] and is contrary to another [26] who observed a higher need for inotropic support in critically ill patients treated with NAC for more than 24 h. Most of our patients had normal blood pressure, but just 6 patients who were hypertensive (140/90 mm Hg) showed a positive correlation between their MAP and microalbumin. Blood pressure can be a cause of microalbuminuria by increasing glomerular filtration pressure resulting in renal damage.

Moreover, this study is in agreement with study of Soltan-Sharifi *et al.* [10] who showed antioxidant potential of NAC responsible for its clinically benefits in patient's outcomes. Suppoering the present data, our recent study also indicated potential of NAC in improving plasma total homocysteine in dialysis patients suffering from chronic kidney disease [27]. In addition, the present results support the role of oxidants in the pathogenesis of ARDS [28-30]. Therefore, improvement of oxidant/antioxidant balance would increase the survival of patients with ARDS who are under oxidative crisis. Small sample size, heterogeneity of patients, NAC dose and administration onset time, and short duration of the study seem responsible for not reaching a significant correlation between MACR and APACHE II or PaO_2/FiO_2. Of course, the present data well support that clinical characteristics of patients in NAC group improve more rapidly than control group just after 24 h treatment. Taken together, it is concluded that the trend toward the improvement in MCR, although was not statistically significant, but it is promising and necessitates further trials.

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