Lack of effect of N-acetylcysteine treatment to ameliorate the progression of multiple organ failure

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ABSTRACT

Objective: To investigate whether prolonged infusion of the oxygen free radical scavenger N-acetylcysteine (NAC) that is commenced immediately after admission to intensive care unit (ICU) could ameliorate the development or progression of multiple organ failure (MOF).

Methods: After receiving ethical committee approval, a prospective randomized, double-blind, placebo controlled study was performed in the Anesthesiology and Reanimation Intensive Care Unit, Hacettepe University Hospital, Ankara, Turkey between December 2002 and May 2003. Twenty-six patients were randomized to receive either NAC in 5% dextrose 40 mg/kg/day or the same volume of 5% dextrose both in 4 divided doses. Two patients were withdrawn due to ICU stay <24 hours. Treatment effect on organ function was assessed by the sequential organ failure assessment (SOFA) scores according to physiological parameters of respiratory, hematological, hepatic, cardiovascular, central nervous system (CNS) and renal system scores that were obtained on admission, then daily. Chi-square, Mann Whitney U tests were used for statistical analysis.

Results: There was no significant difference between the 2 groups in any of the 5 organ dysfunction parameters, total maximum SOFA, delta SOFA length of intensive care stay, days of mechanical ventilation and mortality. In the NAC treatment group, the maximum SOFA coagulation score was higher than the control group ($p<0.05$).

Conclusion: N-acetylcysteine (40 mg/kg/day) that was commenced immediately after admission to ICU did not ameliorate the progression of MOF in this small cohort of patients. We believe routine prophylactic use of low-dose NAC in all critically ill patients does not provide positive protection.

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In critically ill patients, large amounts of oxygen free radicals are released from leukocytes and endothelial cells, causing systemic tissue destruction; and if the host is ill-prepared to protect itself from this onslaught, this oxidant stress may contribute to the development of multisystem organ failure (MOF).[1,2] N-acetyl-L-cysteine (NAC), the N-acetyl derivative of the amino acid L-cysteine-has antioxidant, cytoprotective, and microcirculatory effects that could prove beneficial in these conditions.[3,4] Pharmacologic actions of NAC include the restoration of cellular antioxidant potential by replenishing depleted reduced glutathione stores; the scavenging of oxygen free radicals both directly and as a precursor of glutathione; the inhibition of platelet aggregation, neutrophil activation, tumor necrosis factor (TNF) production, nuclear factor-kappa B activation in sepsis, activation of proinflammatory cytokines such as interleukin-8, cellular apoptosis; and the regeneration of nitric oxide, which is vital for organ perfusion during endotoxic shock and is inactivated

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readily for oxygen free radicals.[1,5-7] But in clinical trials, the potential benefit of NAC in clinical septic shock and MOF remains controversial.[1,5,7-9] To elucidate this controversy of beneficial and adverse effects, the current study was designed with prophylactic and low-dose NAC in critical care patients. The objective was to investigate whether prolonged infusion of the oxygen free radical scavenger NAC that is commenced immediately after admission to intensive care unit (ICU) could ameliorate the development or progression of multiple organ failure, thereby decrease the duration of mechanical ventilation, and ICU stay.

Methods. The protocol was approved by the committee for Ethics of the University Hospital. Informed consent was obtained from the next of kin of each patient. Every patient who was admitted to the Anesthesiology and Reanimation Intensive Care Unit, Hacettepe University Hospital, Ankara, Turkey between December 2002 and May 2003 was entered into the study. Patient with isolated head injury or drug overdose and ICU stay <24 hours were excluded from the study. The design was a randomized, double-blinded, placebo-controlled clinical trial.

Allocation of patients into the treatment group of the placebo group was achieved by envelope randomization.

After randomization, patients received either NAC or the equal volume of placebo 5% dextrose initiated within 4 hours after ICU admission. Investigators and nurses were blinded to the infused drug. The dose of NAC was 40 mg/kg/day (given intravenously in 4 equal dose) in 400 ml of 5% dextrose. Treatment continued until the patient was discharged from the ICU. At admission, simplified acute physiology score II (SAPS II) were computed.[10] In order to assess the organ dysfunction, the sequential organ assessment (SOFA) score was computed at admission and for every 24 hours during the patient's stay in ICU.[11] In SOFA scoring, clinical progress was monitored by patients' respiratory (PAO_2/FiO_2), cardiovascular (hypotension or adrenergic agents administered for at least one hour), renal (serum creatinine or urine output), hepatic (serum bilirubin), hematological (platelet count) and neurological functions (Glasgow coma scale). Maximum organ failure scores were calculated for all the 6 components of the system during the entire ICU stay. The aggregate score (total maximum SOFA score) was calculated summing the worst scores for each of the components. The amount of organ dysfunction/failure appearing after ICU admission (delta SOFA) was evaluated computing the total maximum SOFA score minus the admission total SOFA score.[12]

Statistical Program for Social Sciences 11.0 software was used for statistical analysis. For analysis of categorical data chi-square test was used. Mann-Whitney U test was used to compare the nonparametric data between the 2 groups. $P<0.05$ was considered as significant.

Results. During the study period, 26 patients were recruited. However, 2 patients were withdrawn due to ICU stay of <24 hours. Twenty-four patients were included in the study. The demographic data are seen in **Table 1**. The age, weight and gender were similar between the 2 groups. Simplified acute physiology score II and SOFA scores at admission were not different between the groups. Five patients in the NAC group and 8 patients in the control group were postoperative patients ($p<0.05$). The outcome measures are shown in **Table 2**. Patients in both groups required mechanical ventilation, and intensive care for a similar length of time. The overall courses of the MOF in both groups were not different as evidenced by similar total maximum

Table 1 - The demographic data.

Characteristics	NAC group	Control group	*p* value
Age (years) (median)	69 (16-85)	62.5 (16-80)	0.51
Female/male	5/7	7/5	0.34
Weight (kg) (median)	70 (40-90)	65 (45-90)	0.51
Diabetes mellitus	3	3	1
Malignancy	1	2	1
Congestive heart failure	4	1	0.32
Chronic obstructive airway disease	3	1	0.59
Coronary artery disease	5	1	0.15
Previous ICU stay	7	4	0.41
Emergency admission (median)	9	7	0.33
Hospital stay before ICU admission	1 (0-11)	2 (0-30)	0.59
Diagnoses			0.34
Trauma	1	-	
Heart failure	5	1	
Sepsis	1	1	
Postoperative	3	8	
COAH exacerbation	1	1	
Neurologic	1	1	

NAC - N-acetylcysteine, ICU - intensive care unit,
COPD - Chronic obstructive pulmonary disease

SOFA and delta SOFA scores. There was no statistically significant difference between the 2 groups regarding the progress of the dysfunction of the 5 main organ systems during the ICU stay. In the NAC treatment group, the maximum SOFA coagulation score was higher than the control group ($p<0.05$). The mortality (on leaving the ICU) was higher in the treatment group but it did not achieve a statistical significance.

Discussion. In this study, we evaluated the total maximum SOFA score and delta SOFA of multiple organ dysfunction/failure with the duration of mechanical ventilation, ICU stay, and mortality as measures of outcome. With these measures, we found that NAC (40 mg/kg/day) that was commenced immediately after admission to intensive care unit did not prevent the progression of MOF and did not decrease the duration of mechanical ventilation, ICU stay, and the mortality in our patient cohort. The delta SOFA presents a good correlation with outcome in ICU patients. It has been shown that these can be used to quantify the degree of dysfunction already present on ICU admission, the degree of dysfunction that appears during the ICU stays, the cumulative insult suffered by the patient and the potential influence of therapy.[12] The NAC group was similar to the control group regarding the admission SOFA score, the maximum SOFA score for the 5 organs (respiratory, cardiovascular, renal, hepatic and neurological), total maximum SOFA score and the delta SOFA score showing no outcome benefit of NAC treatment. The only statistically significant difference was observed in the maximum SOFA coagulation score. Coagulation score has a low discriminative power and lower relative contribution to outcome compared to the other organ scores and the total maximum SOFA score.[12] We also believe that this difference in coagulation score is clinically insignificant. As far as we could search in the literature, we could not find any other evidence suggesting NAC treatment related decrease in platelet count.

The discrepancy between encouraging result and negative results associated with NAC treatment may be explained by differences in patient population, dose and timing of intervention and the timing of measurements.[8] The dose of NAC in previous works shows a great variability, from 40 to >480 mg/kg/day.[1,5,9,13] The possible disadvantage of

Table 2 - The outcome measures.

Clinical progress	NAC group (N=12) median (95% CI)	Control group (N=12) median (95% CI)	p value
SAPS II (at admission)	38 (14 - 53)	43 (4 - 72)	0.54
SOFA score (at admission)	4.5 (1 - 9)	4.5 (0 - 12)	0.63
SOFA respiration (at admission)	2 (0 - 4)	3 (0 - 4)	0.41
SOFA coagulation (at admission)	0 (0 - 2)	0 (0 - 2)	0.63
SOFA liver (at admission)	0.5 (0 - 2)	0 (0 - 2)	0.38
SOFA cardiovascular (at admission)	0.5 (0 - 1)	0.5 (0 - 1)	1
SOFA CNS (at admission)	0 (0 - 3)	0 (0 - 4)	0.63
SOFA renal (at admission)	0 (0 - 1)	0 (0 - 4)	0.38
ICU stay (days)	6 (2 - 22)	4 (2 - 23)	0.10
Mechanical ventilation (hr)	50 (13 - 1008)	18 (4 - 720)	0.12
Maximum (max) SOFA	6 (1 - 24)	5 (0 - 13)	0.13
Delta SOFA	1.5 (0 -17)	0 (0 - 4)	0.24
Max SOFA respiration	2.5 (0 - 4)	3 (0 - 4)	0.97
Max SOFA coagulation	1 (0 - 4)	0 (0 - 2)	0.04
Max SOFA liver	2 (0 - 4)	0.5 (0 - 2)	0.11
Max SOFA cardiovascular	1 (0 - 4)	1 (0 - 2)	0.38
Max SOFA CNS	2 (0 - 4)	0 (0 -4)	0.22
Max SOFA renal	0.5 (0 - 4)	0 (0 - 4)	0.27
Infection	7	2	0.08
Hospital stay (days)	33 (8 - 71)	18 (5 - 27)	0.23
Mortality (n)	3	0	0.10

SAPS II - simplified acute physiology score II, SOFA - sequential organ failure assessment, ICU - intensive care unit, CNS -central nervous system, CI - confidence interval

excessive doses could be the formation of toxic intermediate molecules during NAC metabolism, such as thiol and glutathione free radicals, glutathione disulfide, and cysteine.[14] It has been shown in rats that low dose (275 mg/kg) NAC protects against endotoxin toxicity by scavenging hydrogen peroxide, while higher doses may have the opposite effect and increases mortality.[15] We have chosen a much lower dose because a previous study showed that intravenous NAC treatment (40 mg/kg/day for 3 days) improved systemic oxygenation and reduced the need for ventilatory support in patients presenting with mild-moderate acute lung injury subsequent to a variety of underlying diseases. In that study similar to our findings, development of adult respiratory distress syndrome and mortality were also not reduced with NAC therapy.[13]

In another previous randomized, placebo controlled study with a higher dose of NAC (150 mg/kg bolus followed by a continuous infusion of 12 mg/kg/hour for 3-5 days), no outcome benefit was found with NAC treatment. Their result suggested that NAC could be beneficial if the treatment was initiated within 24 hours after hospital admission whilst outcome worsened it the treatment is initiated later.[1] This observation in accordance with similar results had raised the question: Would the administration of NAC given before a defined insult results in an alteration in outcome.[9,16] Therefore, prophylactic use of NAC has also been tried before and during major abdominal surgery and the results did not support the routine prophylactic use of NAC as a free radical scavenger.[16]

In our study, we tried the prophylactic use of NAC in all patients admitted to our ICU initiated as early as possible and continued until discharge from the ICU. Unfortunately, our findings showed that real pre-treatment could not be achieved in our mixed ICU patients because the insult probably occurred well before ICU admission. The high SAPS II and SOFA scores at admission to our ICU suggested that length of illness prior to admission was too long and the NAC treatment was probably late. The hypothesis that the choice of patients with poor residual activity may explain the negative results should be considered.[7,17] Another explanation of our negative findings would be that our case mix was heterogeneous and included both unresponders and responders to NAC therapy. Spies et al[9] reported the results of a trial of high doses of NAC, given within 24 hours of ICU admission in patients with septic shock. The authors did not find positive protection in all patients, but only in a group that they defined as the group of "responders". Unfortunately, we could not detect a group of "responders" in our study due to the small sample size. NAC seems to be more beneficial in early septic shock patients compared to other critically ill patients.[7,18] The explanation for the difference in critically ill patients or septic patients may be that NAC can attenuate a mediator response.[18]

We conclude that prolonged infusion of prophylactic; low-dose (40 mg/kg/day) of NAC that was commenced immediately after admission and continued until discharge from the ICU did not ameliorate the progression of MOF in this small heterogeneous cohort of patients. Furthermore, well controlled, double-blinded, randomized studies are needed to define the dose, duration and the group of "responders" to NAC therapy.

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