N-Acetylcysteine Enhances Recovery From Acute Lung Injury in Man*

A Randomized, Double-Blind, Placebo-Controlled Clinical Study

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Objectives: To determine the effects of intravenous N-acetylcysteine (NAC) on the development of severe adult respiratory distress syndrome (ARDS) and mortality rate in patients with mild-to-moderate acute lung injury and to analyze the duration of ventilatory support and FiO₂ required as well as the evolution of the lung injury score.

Setting: Three university hospital ICUs and one regional ICU in Switzerland.

Patients: Sixty-one adult patients presenting with mild-to-moderate acute lung injury and various predisposing factors for ARDS received either NAC, 40 mg/kg/d, or placebo intravenously for 3 days.

Measurements: Respiratory dysfunction was assessed daily according to the need for mechanical ventilation and FiO₂, the evolution of the lung injury score, and the PaO₂/FiO₂ ratio. The cardiovascular state, liver function, and kidney function were also monitored. Data were collected at admission (day 0), during the first 3 days, and on the day of discharge from the ICU.

Results: The NAC and placebo groups (32 and 29 patients, respectively) were comparable at ICU admission for severity of illness assessed by the simplified acute physiology score (SAPS) (10.8 ± 4.6 vs 10.9 ± 4.8) and lung injury score (LIS) (1.39 ± 0.95 vs 1.11 ± 0.10) (mean ± SD). Three patients in each group developed ARDS. The 1-month mortality rate was 22 percent for the NAC group and 35 percent for the placebo group (difference not statistically significant). At admission, 22 of 32 patients (69 percent) in the NAC group were mechanically ventilated compared with 22 of 29 (76 percent) in the placebo group. At the end of the treatment period (day 3), 5 of 29 (17 percent) in the NAC group and 12 of 25 (48 percent) in the placebo group were still receiving ventilatory support (p = 0.01). The FiO₂ was 0.37 less than admission value (day 0) in the NAC group, and 0.20 less in the placebo group (p < 0.04); the oxygenation index (PaO₂/FiO₂) improved significantly (p < 0.05) from day 0 to day 3 only in the NAC-treated group. The LIS showed a significant regression (p = 0.003) in the NAC-treated group during the first 10 days of treatment; no change was observed in the placebo group. No adverse effects were observed during the treatment with NAC.

Conclusions: Intravenous NAC treatment during 72 h improved systemic oxygenation and reduced the need for ventilatory support in patients presenting with mild-to-moderate acute lung injury subsequent to a variety of underlying diseases. Development of ARDS and mortality were not reduced significantly by this therapy.

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ARDS = adult respiratory distress syndrome; GSH = glutathione; ICU = intensive care unit; LIS = lung injury score; NAC = N-acetylcysteine; NS = not significant; SAPS = simplified acute physiology score

A cute lung injury characterized by a high-permeability, low-pressure pulmonary edema can develop following a number of predisposing diseases resulting in different degrees of respiratory insufficiency. Patients with mild-to-moderate injury could, within this continuum, represent an interesting subset to evaluate a therapeutic approach of lung dysfunction. The pathogenesis of acute lung injury and its severest form, the adult respiratory distress syndrome (ARDS), involves a number of mechanisms and mediators. Toxic oxygen radicals of intra-cellular as well as extracellular origin seem to play an important role.

Oxygen metabolites such as superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), hydroxyl radical (·OH), and hypochlorous acid (HOCl) cause increased vascular permeability in endothelial cell monolayers, in isolated lungs, and in vitro. In human ARDS, increased oxidant activity has been observed in expired breath or in bronchoalveolar lavage (BAL) fluid as well as in granulocytes and red blood cells. In addition, patients with ARDS seem to have a marked deficiency of the tripeptide antioxidant glutathione (GSH) in the extracellular epithelial lining fluid of the lower respiratory tract. Glutathione acts as an antioxidant for H₂O₂. The GSH deficiency observed in ARDS could favor oxidative stress, thus allowing functional and/or morphologic damage in the lower respiratory tract, including an overshooting inflammatory reaction and epithelial and endothelial lesions resulting in pulmonary edema. N-acetylcysteine (NAC) is a GSH agonist, and previous studies have demonstrated that NAC administration increases...
GSH levels in red blood cells, granulocytes, and plasma of patients with ARDS.\textsuperscript{19,20}

Increasing GSH levels in the early phases of acute lung injury with NAC could reduce or limit the extent of epithelial and endothelial damage and improve the clinical course. N-acetylcysteine has been used at high dosages in the treatment of paracetamol intoxication and was well tolerated.\textsuperscript{21}

The purpose of the present study was to assess the effects of NAC on the development of ARDS and mortality in patients with mild-to-moderate acute lung injury associated with known risk factors predisposing to ARDS. Other important end points, such as duration of ventilatory support, FIO\textsubscript{2} requirements, and the clinical course of respiratory function were identified at the end of the investigation and analyzed.

\textbf{Materials and Methods}

\textit{Subjects and Protocol}

During a 12-month period, patients with risk factors known to predispose to the development of ARDS (see below), and presenting with mild-to-moderate acute lung injury, were included in the trial in the four participating intensive care units (ICUs) in Switzerland (Geneva, Lausanne, Basel, Locarno).

In order to collect patients with comparable lung dysfunction for a pharmacologic treatment regimen, we used the expanded definition suggested by Murray et al.,\textsuperscript{22} and only considered patients presenting with an initial lung injury score (LIS) between 0.1 and 2.5. Patients with cardiogenic pulmonary edema and/or chronic heart failure were excluded on the basis of medical history, results of clinical examination, and the use of a pulmonary artery catheter in all unclear situations. The following predisposing factors for the development of ARDS were considered:\textsuperscript{23}

\textit{Sepsis}, defined as proposed by Bone,\textsuperscript{24} was clinical evidence of infection, ie, respiratory rate above 20 cycles/min or minute ventilation over 10 L/min if mechanically ventilated, heart rate more than 90 beats/min, core or rectal temperature outside the range of 35.5\textdegree{} to 38.0\textdegree{}, a white blood cell count above 12,000 or below 4,000/\mu{}l or 20 percent or more immature cells plus evidence of altered organ perfusion (ie, acute change in mental status, PaO\textsubscript{2}/FIO\textsubscript{2}, less than 250, plasma lactate concentration greater than upper limit of normal, and urine output below 0.5 ml/kg of body weight for at least 1 h).

\textit{Multiple trauma} included patients with multiple major fractures (two or more major long bones or unstable pelvic fracture) associated with trauma to another region of the body such as craniocerebral or abdominal, requiring surgical intervention.

\textit{Aspiration} was defined as recent (during the previous 6 h) inhalation of gastric contents, documented by suctioning of gastric material from the bronchial tree or by fiberoptic bronchoscopy showing typical mucosal lesions.

\textit{Necrotizing pancreatitis} was seen as severe abdominal pain, vomiting, increased serum amylase levels, circulatory shock, and a Ranson score of 3 or above.\textsuperscript{25}

\textit{Hemorrhagic shock} was defined as requiring administration of more than 20 U of blood within 24 h.

\textit{Near drowning} was defined as an immersion accident requiring endotracheal intubation.

Patients younger than 16 years, pregnant women, immunocompromised patients, and those with a severe lung injury (LIS > 2.5)\textsuperscript{22} or cardiogenic pulmonary edema were excluded from this trial.

Data were collected at admission to the ICU (baseline), on the first 3 days after admission, and on the day of discharge from the unit. Severity of illness was assessed by the simplified acute physiological score (SAPS).\textsuperscript{26}

Respiratory dysfunction was assessed daily by the requirement for mechanical ventilatory support, the FIO\textsubscript{2} administered, and the evolution of the lung injury score using its first three components (chest radiograph, PaO\textsubscript{2}/FIO\textsubscript{2} ratio, and respiratory system compliance). The FIO\textsubscript{2} was controlled during mechanical ventilation using the built-in oxygen cell of the ventilator. In extubated and spontaneously breathing patients, FIO\textsubscript{2} was regulated by using a Ventimask or a similar device. The FIO\textsubscript{2} obtained was checked regularly with a paramagnetic oxygen sensor (Oxydig, Dräger, Lübeck, Germany).

Mechanical ventilation was initiated and maintained at the discretion of the physician in charge of the patient. The standards for mechanical ventilatory support, oxygen therapy, weaning criteria, and other treatment modalities are applied quite uniformly in the four ICUs participating in the trial. Clinical and biochemical assessment was done regularly. Cardiovascular state, central nervous system, kidney, and liver function were monitored closely.

The patients were randomized to receive either NAC, 40 mg/kg/d, or placebo, administered as a continuous intravenous infusion over the first 3 days after admission to the ICU. This dose and duration of treatment were chosen according to previous work on NAC in ARDS\textsuperscript{27} and in other abnormalities. A dose of 40 mg/kg is one order of magnitude higher than what is normally applied in regimens of chronic respiratory disease and yet one order lower than the dose for paracetamol intoxication. We believed that this dose could offer sufficient efficacy as a preventive therapy in ARDS without exposing to drug toxicity.\textsuperscript{28} N-acetylcysteine and placebo were packed in similar numbered vials allowing randomization and double-blind administration.

Informed consent was obtained from the patient or, if this was not possible because of the clinical condition, from the next of kin. The protocol was submitted to and approved by the committees for ethics in human research of the university hospital of Basel.

\textbf{Table 1—Characteristics of Patient Groups, SAPS Scale and Lung Injury Score (LIS) at Admission to the ICU\textsuperscript{29}}

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N-acetylcysteine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>24/8</td>
<td>23/6</td>
</tr>
<tr>
<td>Age, y</td>
<td>46.6 ± 18.7</td>
<td>48.1 ± 21.9</td>
</tr>
<tr>
<td>Range</td>
<td>16-76</td>
<td>16-76</td>
</tr>
<tr>
<td>Primary risk factors (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Multiple trauma and aspiration</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Sepsis and aspiration</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Aspiration</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Near drowning</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Necrotizing pancreatitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Associated diseases and complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Shock</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Septicemia</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Simplified acute physiology score\textsuperscript{30}</td>
<td>10.8 ± 4.60</td>
<td>10.9 ± 4.80</td>
</tr>
<tr>
<td>LIS\textsuperscript{31}</td>
<td>1.39 ± 0.95</td>
<td>1.11 ± 1.08</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU stay, days, mean ± SD</td>
<td>11.3 ± 10.5</td>
<td>12.2 ± 9.6</td>
</tr>
<tr>
<td>Development of ARDS, n</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mortality rate, n (%)</td>
<td>7 (22)</td>
<td>10 (35)</td>
</tr>
</tbody>
</table>

* Differences between the two patient groups are statistically not significant.
Statistics Methods

Initial homogeneity assessment of the two groups was performed by t test and χ² analysis. The before and after comparisons were done with the sign test, the paired t test, and the Wilcoxon-Pratt test depending on the distribution of the data. Between-group comparisons were performed with the χ² test, the Student t test, and the Wilcoxon-Mann-Whitney U test according to the distribution of the data. Data are presented as mean values ± standard deviations unless specified otherwise.

Results

Characterization of Patients

A total of 61 patients (47 men and 14 women) were recruited for the study (Table 1). All were considered evaluable for data analysis. Thirty-two patients received NAC and 29 received placebo. The two groups were well matched for demographic characteristics on trial entry. The SAPS for severity of disease was 10.8 ± 4.6 in the NAC group and 10.9 ± 4.8 in the placebo group (± SD, not significant [NS]). On admission, the lung injury score was 1.39 ± 0.95 in the NAC group, a value not significantly different compared with the placebo group of 1.11 ± 1.08. Risk factors and associated conditions were similar in the two groups. Three patients in each group developed severe lung injury (ARDS) defined as a LIS above 2.5. Seven of 32 patients (22 percent) in the treatment group and 10 of 29 (35 percent) in the placebo group died (NS). During the study, adverse events due to NAC were not detected.

Ventilatory Support, FIO₂, Lung Function

Twenty-two patients in each group (69 percent in the NAC and 76 percent in the placebo group) required ventilatory support at ICU admission (day 0); at day 3, the percentage of patients receiving ventilatory support was significantly reduced in the treated group from 69 to 17 percent (p = 0.01), whereas in the placebo group this decrease (from 76 to 45 percent) was not significant. p = 0.01 between groups (Fig 1). At day 0, there was no significant difference between the two groups with regard to FIO₂ administered. At day 3, the FIO₂ was significantly decreased in the NAC group (0.29 ± 0.09 vs 0.48 ± 0.24 at admission; p < 0.01) whereas in the placebo group there was no significant decrease (0.35 ± 0.11 vs 0.45 ± 0.20). The difference in FIO₂ between the two groups was significant on day 3 (p < 0.05). The oxygenation index PaO₂/FIO₂ was similar at admission for both groups (255 ± 113 mm Hg in the NAC vs 248 ± 99 mm Hg in the placebo group, NS) and increased significantly in the NAC group reaching 294 ± 99 mm Hg on day 3 (p < 0.05). No significant change was noted in the placebo group (Fig 2). There was no statistical difference in PaO₂/FIO₂ between the NAC- and placebo-treated patients. The lung injury score decreased in the NAC group from 1.39 ± 0.95 to 0.67 ± 0.70, p < 0.01, between ICU admission and day 10. No significant change was observed in the placebo group. At ICU admission, the mean chest radiograph score was higher in the NAC than in the placebo group (1.8 ± 1.1 vs 1.1 ± 1.1; p < 0.05). Up to day 3 this score increased in the placebo group (p < 0.05), whereas it did not change significantly in the NAC group up to day 3, but decreased until the discharge from the ICU (from 1.8 ± 1.1 at admission to 1.1 ± 1.1, p < 0.01).

Discussion

Despite major improvements in patient care, ARDS still remains a formidable clinical challenge and carries

Enhanced Recovery From Acute Lung Injury (Suter et al)
a high mortality rate. Recent clinical studies suggest that patients with ARDS undergo relevant oxidative stress. Toxics oxygen products cause cellular and subcellular damage and activate epithelial cells, macrophages, or endothelial cells. Oxygen radicals are also recognized as mediators between primary and secondary effectors, either directly or via cytokine release (i.e., tumor necrosis factor) with subsequent formation of reactive oxygen. Thus, oxygen-free radicals are important proinflammatory agents and it seems desirable to control their activity in states of overshooting inflammation. Endogenous antioxidants and particularly glutathione (GSH) normally constitute an effective control of toxic oxygen. Glutathione is detected in high concentrations in the extracellular epithelial lining fluid of the lower respiratory tract of normal subjects and could act as a first-time scavenger of toxic oxygen intermediates and protect against lung cell damage and injury. Patients with severe acute lung injury of the ARDS type have a marked decrease of GSH in epithelial lining fluid, plasma, and blood cells. Glutathione depletion in plasma and granulocytes in ARDS is reversible by N-acetylated glutathione rescue.

The present trial examines the effects of NAC in patients presenting with mild-to-moderate acute lung injury. At ICU admission, our two groups were similar for severity of illness and lung injury score. We were unable to find a preventive effect of NAC on the progression to ARDS. Survival had a tendency to be higher in the NAC group. N-acetylcysteine may have positive hemodynamic effects in critically ill patients, improvement in cardiac output, systemic oxygen transport, and consumption. The mechanisms involved in these changes are not entirely clear. N-acetylcysteine possibly restores the decreased activity of endothelium-derived relaxing factor, thereby improving microcirculation. The most interesting finding of our study is the improvement seen in oxygenation index and LIS, which are sensitive markers of the severity of acute respiratory failure and prognosis. Fewer patients in the NAC group were receiving mechanical ventilatory support at day 2 and 3 and this had a tendency to have a shorter ICU stay (median 7 days vs 10 days for the placebo group).

In conclusion, the present study suggests that early intravenous administration of NAC in patients with mild-to-moderate acute lung injury improves pulmonary gas exchange and may reduce the duration of mechanical ventilatory support. However, the number of patients included is small and the causes of acute lung injury is heterogeneous. Further and larger trials have to be done to define if this therapy can prevent ARDS and improve outcome.

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