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# N-acetylcysteine to prevent multisystem organ failure

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## Keywords

Antioxidants, critical illness, glutathione, multiple organ dysfunction score, multisystem organ failure, N-acetylcysteine, oxidative stress, oxygen free radicals, respiratory burst, sepsis

# Comments

This randomized, double blind placebo control trial was well designed including power analysis of the study. From the results it seems that there may be a role for NAC in a subgroup of ICU patients, although from these results the only factor which appears to identify such patients is length of hospital stay. This difference seen on subgroup analysis between patients admitted to ICU either within or after 24 h of hospital admission highlights our poor fundamental understanding of sepsis and multi-organ failure and may suggest a difference in patient response to the inflammatory insult from a variety of diseases. On the basis of these results, the use of NAC outside of clinical trials is difficult to justify.

# Introduction

Increasing interest in the pathophysiology of sepsis and multi-organ failure has focused on the role of oxygen free radicals. Important endogenous mechanisms exist to protect against oxidative damage caused by free radicals. The main mechanism is the detoxification of free radicals by reduced glutathione. It has been demonstrated that in sepsis the levels of glutathione are decreased, and this depletion is associated with increased mortality. N-acetylcysteine (NAC) has been used as a free radical scavenger, working either by direct scavenging or by increasing intracellular stores of glutathione. Several previous trials have demonstrated an improved outcome in adult ICU patients with respiratory failure and sepsis when treated with NAC.

# Aims

To determine whether NAC, administered as a prolonged infusion immediately after ICU admission, prevents or slows down multi-organ failure and reduces the mortality rate.

# Methods

Ethics Committee approval was given for this prospective, randomized, double blind trial on a six-bed ICU in a teaching hospital. Every patient admitted to the unit over a 15-month period who required mechanical ventilation and the support of two or more organ systems could be included in the study. Patients with chronic organ insufficiency before their admission, isolated head injury or drug overdose were excluded.

The eligible patients received either NAC or an equal volume of 5% dextrose as placebo. The dose of NAC was given as a bolus of 150 mg/kg in 250 ml of 5% dextrose followed by an infusion of 12 mg/kg/h in 500 ml of 5% dextrose for 24 hours. Infusion was continued for three to five days. Data were collected on patient demographics, multi-organ dysfunction score (MODS), mortality, and length of inotrope and ventilatory support.

# Results

A total of 100 patients were recruited (50 in each group). Nine patients from the treatment group and five in the control group were withdrawn from the study because their ICU stay was less than 48 hours. The groups were well matched in term of patient demographics, APACHE II and MODS on admission.

Outcome measures used were days of inotropic support, days of mechanical ventilation, duration of ICU stay and ICU mortality. MODS were collected daily for both groups. In all these measures there were no statistically significant differences between the treatment and control groups.

The two groups were subdivided into patients that were admitted to the ICU within and after 24 hours of hospital admission. When analysing these subgroups, the authors found a non significant improvement in mortality in the NAC-treated group who were admitted to ICU within 24 h. However, the NAC-treated patients admitted to the ICU more than 24 h after hospital admission had a significantly higher mortality rate.

# Discussion

The authors report that NAC treatment made no significant difference in outcome in this ICU population. Their results also indicate that the initiation of NAC more than 24 h after hospital admission may be potentially harmful.

The mechanism by which NAC exerts an effect is unknown. In animal models of sepsis, NAC pre-treatment has been shown to significantly suppress neutrophil oxidative burst activity and cause delayed bacterial elimination. There are increasing suggestions that the high mortality rate seen with sepsis and

multi-organ failure is not related to the bacteria themselves but to the response of the host to this inflammatory insult.

The authors add that this study supports the need for further research into the early use of NAC in critically ill patients. They also emphasise that to reach a firm conclusion on the use of NAC we need a better understanding of the role of oxygen free radicals and their interaction with NAC in critically ill patients.

## References

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