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ORIGINAL ARTICLE

# Efficacy and safety of acetylcysteine in ''non-acetaminophen'' acute liver failure: A meta-analysis of prospective clinical trials

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**Summary**
*Background:* Acute liver failure (ALF) is a rare but highly mortal condition without liver transplantation (LT). N-acetylcysteine (NAC), a glutathione precursor that detoxifies the reactive metabolite of acetaminophen and replenishes hepatic glutathione stores, is a highly effective drug for the prevention of ALF caused by acetaminophen. However, therapeutic use of NAC in non-acetaminophen-induced ALF (NAI-ALF) including alcohol intoxication, hepatitis virus infection, or drug and toxin-related hepatotoxicity is still inconclusive. The aim of this article is using meta-analysis method to analyze recent prospective clinical trials for the safety and efficacy of NAC in patients with ALF not caused by acetaminophen poisoning.
*Methods:* Prospective clinical trials comparing efficacy and safety between NAC and control in the treatment of NAI-ALF were identified by searching Pubmed (2000—2014) and EMBASE (2000—2014) using the search terms acetylcysteine or NAC and NAI-ALF. The primary outcome was overall survival. Secondary outcomes included liver transplantation-free survival, post transplantation survival, length of ICU and hospital stays, and the relationship with coma grade. The safety profiles were also analyzed.
*Results:* Four clinical trials were selected for meta-analysis. A total of 331 patients receiving treatment with NAC (oral or intravenously) and 285 patients in control group were included for meta-analysis. No statistical difference was identified between NAC group and control group for overall survival [236/331 (71%) vs 191/285 (67%); 95% CI 1.16 (0.81—1.67); $P = 0.42$]. However, there were significant differences between NAC group and control group regarding the survival with native liver [112/273 (41%) vs 68/226 (30%); 95% CI 1.61 (1.11—2.34); $P = 0.01$] and post-transplantation survival [78/91 (85.7%) vs 50/70 (71.4%); 95% CI 2.44 (1.11—5.37); $P = 0.03$]. The identified side effects of NAC included nausea, vomiting, and diarrhea or constipation. Rarely, it could cause rashes, fever, headache, drowsiness, low blood pressure, and elevated

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serum transaminase levels in a patient with cystic fibrosis. At the dose used for acetaminophen toxicity, acetylcysteine does not have hepatotoxic effects.
*Conclusion:* NAC is safe for NAI-ALF. It can prolong patients' survival with native liver without transplantation and survival after transplantation, but it cannot improve the overall survival.


## Introduction

Acute liver failure (ALF) is a life threatening disease, usually caused by alcohol intoxication, hepatitis virus infection, or hepatotoxic drugs and toxins. A recent survey has shown that acetaminophen overdose is the most frequent cause of ALF in the US [1]. Acetylcysteine (NAC) is the N-acetyl derivative of the amino acid cysteine and is the agent of choice to prevent hepatotoxicity associated with acetaminophen overdose. However, although NAC is currently used as off label for acetylcysteine in non-acetaminophen induced ALF (NAI-ALF), the efficacy is still inconclusive.

A number of double blind, randomized and multi-center clinical trials have been conducted to assess the efficacy of NAC on NAI-ALF in both adults and children. The first clinical trial was started in 1998 by the Acute Liver Failure Study Group, funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health. It is a prospective, randomized, double-blind, placebo-controlled trial of NAC for adult NAI-ALF patients, which was conducted at 24 participating sites in the United states for eight years from 1998 to 2006 [2]. There was no difference in the overall survival at three weeks between NAC (70%) vs placebo groups (66%) ($P = 0.238$). However, transplant-free survival was significantly better in NAC patients with coma grades I—II who received NAC compared with placebo (52% vs 30%, $P = 0.010$); however, no difference was found in coma grades III—IV ($P = 0.912$). Another prospective study that enrolled 47 adult NAI-ALF patients also showed similar results, in which 22 patients (47%) survived in NAC group and 12 (27%) in control group ($P = 0.05$), indicating that NAC caused reduction in mortality [3].

However, other studies in pediatric patients demonstrated controversial results [4,5]. The results of the study by Singh et al. [4] do not support the use of NAC for NAI-ALF because the survival between the NAC (73%) and placebo (82%) treatment groups was not statistically different. The 1-year transplantation-free survival was significantly lower ($P = 0.03$) in those who received NAC (35%) than those who received placebo (53%). Another retrospective study showed that NAC was associated with a shorter length of hospital stay, higher incidence of native liver recovery without transplantation, and better survival after transplantation [5].

There are a few causes for the discrepancy among the studies. The two studies in children groups are limited by the historical control groups in which the patients were not treated at the same time as in NAC group. Also, the patient population in Mumtaz et al.'s study [3] showed that the patients in NAC group were younger and their disease was more severe compared to the control group. Therefore, in order to draw solid conclusions about the efficacy of NAC for NAI-ALF patients, there is a need for further clinical trials in a larger number of patients.

The aim of this article is to evaluate the safety and efficacy of NAC in patients with ALF not caused by acetaminophen poisoning using meta-analysis method.

## Methods

### Database and search strategy

We searched the following database for relevant studies: PubMed (from 2000 to April 2014) and EMBASE (from 2000 to April 2014). Search terms used for PubMed are: ''NAC'' and ''acute liver failure'' or ''acetylcysteine'' and ''acute liver failure''.

### Study selection criteria and Quality assessment

Eligible studies were selected based on the following criteria:

- study design: prospective study;
- subjects: patient with NAI-ALF, including adults and children who were up to 18-year old
- intervention: NAC administered orally or intravenously.

Authors independently conducted study selection based on these criteria.

### Primary and secondary outcomes

The primary outcome for the assessment of NAC use was the overall survival. The secondary outcomes included the safety of NAC, transplant-free survival and survival post transplantation.

### DATA extraction and statistical analysis

The following information was extracted from selected studies: authors, publication year, study design, number of patients analyzed, treatment regimen, primary and secondary outcomes. All statistical analyses were performed using the Review Manager, version 5.1.0 (Cochrane Collaboration, Oxford, UK). Dichotomous outcomes were presented as odds ratio with a 95% confidence interval (CI). A $P$ value $\leq 0.05$ was considered statistically significant. Random-effects models were used for the meta-analysis in