Research Article

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Enteral nutrition with or without *N*-acetylcysteine in the treatment of severe acute alcoholic hepatitis: A randomized multicenter controlled trial

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Background & Aims: Severe acute alcoholic hepatitis is associated with a high mortality rate. Oxidative stress is involved in the pathogenesis of acute alcoholic hepatitis. Previous findings had also suggested that enteral nutritional support might increase survival in patients with severe acute alcoholic hepatitis. Therefore, the aim of the present study was to evaluate the efficacy of *N*-acetylcysteine in combination with adequate nutritional support in patients with severe acute alcoholic hepatitis.

Methods: Patients with biopsy-proven acute alcoholic hepatitis and mDF $\geqslant$32 were randomized to receive *N*-acetylcysteine intravenously or a placebo perfusion along with adequate nutritional support for 14 days. The primary endpoint was 6-month survival; secondary endpoints were biological parameter evolution and infection rate.

Results: Fifty-two patients were randomized in the study (28 into the *N*-acetylcysteine arm, 24 into the control arm), and among them, five were excluded from the analysis for protocol violation. The two groups did not differ in baseline characteristics. Survival rates at 1 and 6 months in *N*-acetylcysteine and control groups were 70.2 vs. 83.8% ($p = 0.26$) and 62.4 vs. 67.1% ($p = 0.60$), respectively. Early biological changes, documented infection rate at 1 month, and incidence of hepatorenal syndrome did not differ between the two groups.

Conclusions: In this study, high doses of intravenous *N*-acetylcysteine therapy for 14 days conferred neither survival benefits nor early biological improvement in severe acute alcoholic hepatitis patients with adequate nutritional support. However, these results must be viewed with caution, since the study suffered from a lack of power.

Keywords: Alcoholic hepatitis; *N*-acetylcysteine; Enteral nutrition; Oxidative stress.

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Abbreviations: AAH, acute alcoholic hepatitis; ALD, alcoholic liver disease; DF, discriminant function; NAC, *N*-acetylcysteine; MELD, model for end-stage liver disease; HRS, hepatorenal syndrome; INR, international normalized ratio; ROS, reactive oxygen species; GSH, glutathione; HVPG, hepatic venous pressure gradient.

Introduction

Acute alcoholic hepatitis (AAH) is the most severe form of alcoholic liver disease (ALD) and is characterized by hepatocellular necrosis, ballooning degeneration, an inflammatory reaction with numerous polymorphonuclear leukocytes and fibrosis [1,2].

Severe AAH is identified by the presence of encephalopathy and/or a discriminant function (DF) $\geqslant$32 [3,4]. DF $\geqslant$32 prospectively identifies patients with a 40–50% risk of dying within 2 months [5]. Treatment of AAH consists of abstinence from alcohol and correction of nutritional deficiencies [6]. Corticosteroids are generally recommended in patients with severe AAH. Indeed, a recent analysis of individual data from the last three randomized-controlled trials showed significantly higher 1-month survival in corticosteroid-treated patients than in controls with severe AAH [7]. However, corticosteroids do not improve long-term survival in patients with severe AAH [7]. Therefore, the search for alternative therapeutic options is crucial. Antioxidant therapy is of theoretical interest in the treatment of alcoholic hepatitis due to increasing evidence that oxidative stress is a key mechanism in alcohol-mediated hepatotoxicity [6,8]. Ethanol consumption results in depletion of endogenous antioxidant capacities, and patients with ALD show evidence of antioxidant deficiencies [9]. In particular, chronic ethanol consumption has been reported to cause selective deficiency in the availability of reduced glutathione (GSH) in mitochondria due to impaired functioning of the specific mitochondrial carrier that translocates GSH from the cytosol into the mitochondrial matrix [10,11].

Due to its effect on glutathione store restoration, and consequently, upon limitation of oxidative stress, *N*-acetylcysteine (NAC), which has an excellent tolerance and safety profile, is a potential therapeutic agent in the treatment of AAH. NAC also inhibits apoptosis and proinflammatory cytokine production [12,13].

In addition, patients with severe AAH are frequently malnourished and may often remain anorectic for several weeks [14]. Recent evidence has indicated that adequate enteral nutritional support might have an important impact on long-term survival in these patients [15]. In this context, we hypothesized that NAC in association with adequate nutritional support, might be beneficial in severe AAH.

Patients and methods

Patient selection and treatment

This Belgian multicenter, single-blinded, controlled trial under the auspices of the Belgian Association for the Study of the Liver (BASL) recruited patients from three participating centers (Erasme University Hospital, Brussels; Brugmann Hospital, Brussels; Ghent University Hospital, Ghent). Inclusion criteria included biopsy-proven alcoholic hepatitis (defined by the presence of satellitosis) and severe disease defined by a DF $\geqslant$32 at baseline [total bilirubin in mg% + 4.6 $\times$ (patient prothrombin time – control prothrombin time in seconds)]. Exclusion criteria included neoplastic disease compromising 6-month survival, positive HIV serology, and hepatorenal syndrome (HRS) at randomization [16]. All patients were tested for hepatitis C, hepatitis B, and HIV.

Patients were centrally randomized by blocks of six (one separate set of randomization envelopes for each center) into two groups: NAC or the control group. The study was single-blinded for the patient. Medical and paramedical staffs was informed whether the patient received NAC or control perfusion. Management of all patients included adequate enteral nutrition support. In addition to the usual meals, patients received enteral nutrition of at least 27 kcal/kg/day for 14 days in the form of commercially available mixtures (the type of mixture was not standardized). Whenever possible, enteral nutrition was given orally. If the patient did not consume the expected number of calories, placement of a feeding tube was performed. In addition, supplements of vitamin B1, B6, folic acid, phosphorus, zinc, and magnesium were given during the study. The NAC group received 300 mg/kg of *N*-acetylcysteine (Lysomucil®, Zambon Pharma, Belgium) diluted in 5% glucose adjusted to 500 ml/day intravenously for 14 days. Patients in the control group received the same amount of 5% glucose for 14 days. Patients were assessed every 3 days for 2 weeks, then at 1 month, and every month thereafter. The primary endpoint was 6-month survival. Secondary endpoints were rate of infection and clinical and biological parameters.

The study protocol was approved by the Ethics Committees of the participating centers. Written informed consent was obtained from each participating patient.

Statistical analysis

Based on a 6-month mortality of 50% and an expected reduction of 50% (to 25%) in the NAC group, 43 patients had to be included in each arm, using an α-error of 0.05 and a β-error of 0.2. An intermediate analysis was planned after inclusion of half of the patients. Data are expressed as median (range). Continuous variables were compared using the Mann–Whitney *U*-test. The predictive values of clinical and laboratory parameters for survival were univariately assessed by comparing their Kaplan–Meier survival curves with the log-rank test. The cut-off level chosen for the continuous variables was the median value of the quantitative variables or an already validated cut-off. To identify independent predictors of survival, variables achieving significance (p <0.05) in univariate analysis were then included in a proportional hazards Cox regression model. When a composite score was tested, factors included in it were not further considered in multivariate analysis. Calculations were performed using SPSS 15.0 software (Chicago, IL, USA).

Results

Among 54 eligible patients, 52 were randomized between September 2000 and November 2005 (28 into the NAC group and 24 into the control group). Among these 52 patients, five were excluded from analysis because of a baseline DF <32. From the 47 analyzed patients, 27 were randomized into the NAC group and 20 into the control group (Fig. 1). No significant difference between the NAC and control groups was observed for age, gender distribution, DF, model for end-stage liver disease (MELD) score, total bilirubin, prothrombin time, creatinine, albumin, AST, white blood cell count, hepatic venous pressure gradient (HVPG), or delay between admission and randomization. The percentage of patients with ascites and infection was not statistically different between the two groups (Table 1). Four patients had positive HCV antibodies (one in NAC group, three in control group). All patients were hepatitis B surface antigen negative. Liver histology was available for all patients and cirrhosis was present on pathological examination in 81% of them. One patient in the NAC group had baseline serum creatinine of 5.42 mg/dl, considered as acute tubular necrosis secondary to severe sepsis (which was resolved at randomization). Among the 47 patients, three were shifted to steroids, two after completion of 14 days of therapy (one in NAC group, one in control group). The third had initially been randomized into the control group but was shifted to steroids 6 days after randomization (at the time of steroid initiation, therapy according to protocol had been stopped and treatment was given at the discretion of the investigator). Treatment was prematurely discontinued before day 14 in one patient (NAC group) because of septic shock. No adverse effects were attributable to NAC therapy.

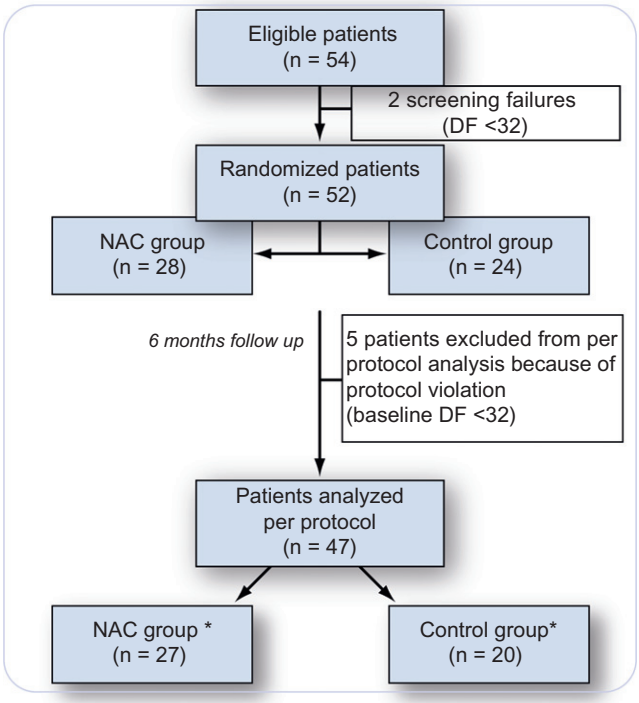

Fig. 1. Trial profile. NAC, *N*-acetylcysteine. *3 patients were shifted to steroids (1 in NAC group, 2 in control group). These patients were excluded from per protocol analysis, when shifted to steroids.

Patients were followed up until death or censored at 6 months. In per-protocol analysis, the 1- and 6-month survival rates were not significantly different between patients in the NAC and control arms (70.2% vs. 83.8%, p = 0.26 and 62.4% vs. 67.1%, p = 0.60, respectively) (Fig. 2). The evolution of bilirubin and the MELD score did not significantly differ between the