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The efficacy of N-acetylcysteine as a hepatoprotective agent in liver transplantation

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Abstract One of the most common complications after liver transplantation is primary graft dysfunction which results from severe deterioration of the microcirculation. The data obtained from our experimental studies indicate that N-acetylcysteine (NAC) is able to reduce the severity of ischemia/reperfusion injury and improves postoperative graft function after liver transplantation in rats. The aim of this pilot study was to evaluate the efficacy of NAC as a hepatoprotective agent under clinical conditions. A group of 30 liver transplanted patients were treated with NAC, and 30 patients (control group) were treated with a 5% solution of glucose only. In the NAC group we observed a distinct reduction in ischemia/reperfusion injury and improved liver function with less elevated peak transaminases, better macrocirculation, improved liver synthesis function and a lower incidence of primary nonfunction compared with the control group. We conclude that NAC is a very promising substance for reducing graft dysfunction in clinical liver transplantation.

Key words Liver transplantation · Ischemia/reperfusion injury · N-acetylcysteine · Primary nonfunction

Introduction

In recent years, the use of standardized preservation solutions in clinical liver transplantation has resulted in a distinct improvement in postoperative graft function. Nevertheless, severe disturbances of the micro- and macrocirculation, induced by so-called ischemia/reperfusion injury, still occur especially after a prolonged cold and warm ischemic period. These severe alterations of the hepatic micro- and macrohemodynamics are the major cause of postoperative liver dysfunction, or even nonfunction, and therefore the major reason for early postoperative mortality. Recent observations in different animal models have shown an improvement in hepatic macro- and microcirculation as well as liver function and survival rate after warm liver ischemia or liver transplantation with the use of N-acetylcysteine (NAC) [2, 3]. In our own experimental studies using intravital microscopy, we have clearly demonstrated an improvement in sinusoidal and acinar perfusion, a reduction in leukocyte adherence in sinusoids and postsinusoidal venules and increased postoperative bile flow indicating improved graft function after orthotopic liver transplantation in rats following the use of NAC [6]. These encouraging results prompted us to evaluate the efficacy of NAC as a hepatoprotective agent in liver-transplanted patients in a clinical pilot study.

Table 1 Analysis of the clinical and laboratory data (values are means ± SEM)

	Donor age* (years)	Recipient age* (years)	Ischemic period (min)	Portal vein flow (ml/min/ 100 g liver)
NAC	43.8 ± 1.9*	48.1 ± 1.9*	694 ± 27	126.3 ± 7.5**
Control	37.6 ± 2.6	41.2 ± 2.7	634 ± 23	100.7 ± 9.5

	Hepatic artery flow (ml/min/ 100 g liver)	Peak AST (U/l)	Peak ALT (U/l)	PNF (%)
NAC	28.1 ± 2.3	773 ± 133	775 ± 165	0
Control	25.4 ± 2.3	1102 ± 225	1094 ± 179	10

	Coagulation factors (IU/24 h)	Histological grade of reperfusion injury			
		None	Slight	Moderate	Severe
NAC	1635 ± 299	55.2%	31.0%	13.8%	0%
Control	2906 ± 965	55.2%	27.6%	3.4%	13.8%

* $P < 0.05$, Student's t-test, Mann-Whitney rank sum test;
** 0.05, Student's t-test

Materials and methods

The efficacy of NAC was tested in a prospective, randomized pilot study approved by the Ethics Commitee of the Ärztekammer Baden-Württemberg. In this trial, 60 orthotopic liver transplantations were performed in 57 patients between January 1996 and August 1997. The underlying liver diseases were: fulminant hepatic failure ($n = 7$), chronic viral hepatitis ($n = 15$), alcoholic cirrhosis ($n = 13$), primary sclerosing cholangitis ($n = 4$), hepatocellular carcinoma ($n = 6$), primary biliary cirrhosis ($n = 2$) and 'others' ($n = 7$). Six of the transplantations were retransplantations. The transplantations were performed according to the Heidelberg protocol. Of the 60 harvested grafts, 58 were stored in UW solution and two were stored in HTK solution. A group of 30 patients were treated with NAC (Fluimucil, Antidot, Zambon, Gräfelfing, Germany) according to the following schedule. Before completing the anastomosis of the portal vein, the graft was rinsed with 1 l Ringer's solution containing 1000 mg/l NAC. Shortly before reperfusion, 150 mg/kg NAC dissolved in 100 ml 5% glucose solution was administered to the donor systemically over 15 min. Then 50 mg/kg NAC dissolved in 250 ml 5% glucose solution was administered over 4 h. This was followed by treatment of the recipient for 16 h with 100 mg/kg NAC dissolved in 500 ml 5% glucose solution. The control group ($n = 30$) was treated with the same volume of 5% glucose solution but without NAC.

The variables in this study were: intraoperative Doppler measurements of the hepatic artery and portal vein flow, peak AST, peak ALT, histological classification of reperfusion injury, incidence of primary graft nonfunction (PNF) and the need for postoperative substitution with coagulation factors within the first 24 h. The donor and recipient ages, the preservation time, the diagnosis of the recipient and possible side effects of the NAC treatment were also recorded. Statistical comparisons between the groups were performed using Student's t-test for normally distributed data or the Mann-Whitney rank sum test for non-normally distributed data.

Results

The results of this study are summarized in Table 1. All data are expressed as means ± SEM. Although the conditions were more unfavorable in the treatment group (significantly higher donor and recipient ages and longer preservation time of the grafts on average), a distinct reduction in ischemia/reperfusion injury and improved liver function were observed in patients treated with NAC. The intraoperative flow data indicated a better macrocirculation with a significantly higher portal vein flow (126.3 ± 7.5 versus 100.7 ± 9.5 ml/min per 100 g of liver) and a slightly improved arterial flow (28.1 ± 2.3 versus 25.4 ± 2.3 ml/min per 100 g of liver) when using NAC. PNF was observed in 10% of the subjects in the control group, whereas no PNF occurred in the NAC group. The reduction in postoperative liver damage in the NAC group was reflected by lower peak transaminases (AST 773 ± 133 versus 1102 ± 225 U/l; ALT 775 ± 165 versus 1094 ± 179 U/l) and improved liver function indicated by a reduced need for the substitution of coagulation factors within the first 24 h postoperatively (1635 ± 299 versus 2906 ± 965 IU/24 h). The histological evaluation of the reperfusion injury revealed less severe destruction of the hepatic microarchitecture after administration of NAC. No side effects of NAC treatment were observed in this study.

Discussion

The results of our clinical pilot study confirm the findings obtained using animal models, indicating that NAC might be very useful in reducing ischemia/reperfusion injury after orthotopic liver transplantation thus improving postoperative graft function without any obvious side effects. In this pilot study, significant results could not be expected because of the small number of patients and the high variability of the data. Previous reports indicate that different properties of NAC interfere synergistically with the cascade of pathomechanisms of ischemia/reperfusion injury after liver transplantation. NAC is a very powerful oxygen radical scavenger [3], it seems to enhance the vasodilative properties of the NO molecule [1] and it inhibits the activation of thrombocytes, neutrophils and monocytes which play a dominant role in the pathomechanism of ischemia/reperfusion injury [4, 5].

We conclude that NAC seems to be a promising substance for reducing ischemia/reperfusion injury in clinical liver transplantation. Prospective, randomized multicenter studies should be carried out to evaluate the clinical significance of our observations.

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