Role of *N*-acetylcysteine treatment in non-acetaminophen induced acute liver failure

PICU

Dr. Nguyen Duy Tan

Introduction

Pediatric acute liver failure (PALF) is a complex, rapidly progressive clinical syndrome.

- IN the United States 17/100,000 per year, but in children is unknown.
- PALF 10% of pediatric liver transplants (LT).

Lutfi R, Abulebda K (2017), “” Intensive Care Management of Pediatric Acute Liver Failure””. *J Pediatr Gastroenterol Nutr*, 64(5), pp 660-670

Introduction

Cause of ALF:

TABLE 1. Causes of ALF (4,5)

Diagnosis	Infants younger than 7 months, % (n = 149)	Children older than 7 months, % (n = 554)
Indeterminate (incomplete evaluation)	61 (40.9)	268 (48.4)
Drug toxicity	3 (2)	108 (19.5)
Autoimmune hepatitis	0 (0)	48 (8.7)
Metabolic	27 (18.1)	41 (7.4)
Infections	20 (13.4)	25 (4.5)
Other diagnosis	38 (25.5)	64 (11.6)

ALF = acute liver failure.

Lutfi R, Abulebda K (2017), "" Intensive Care Management of Pediatric Acute Liver Failure"". *J Pediatr Gastroenterol Nutr*, 64(5), pp 660-670

Introduction

Diagnosis:

- Onset: Eight weeks
- Biochemical evidence (↑ AST, ALT, billirubin)
- Not corrected by vitamin K
- Clinical evidence of encephalopathy – Required for participants with an INR >1.5 but <2.0; not required if coagulopathy is severe (PT ≥20 s or INR ≥2.0).

Squires H (2019),” Acute liver failure in children: Etiology and evaluation”, uptodate.

Management ALF

- Large supportive unless conditions identify
- Early referral to a liver transplantation (LTx) center, associated with improved survival in PALF.
- Long term outcomes following LTx for PALF are poor compared to other indications for LTx, hence the need to identify treatments that improve survival.
- N-acetylcysteine (NAC), used for treating acute acetaminophen (APAP) toxicity, has been used to treat non-APAP PALF but has not been rigorously

N-acetylcysteine

- scavenges free oxygen radicals and replenishes cellular mitochondrial and cytosolic glutathione stores.
- Suppressing the activation of macrophages and neutrophils, blocking the release of inflammatory cytokines.
- N-acetylcysteine (NAC) used for treating acute acetaminophen toxicity: antidote and antioxidant .

IMPROVEMENT BY ACETYLCYSTEINE OF HEMODYNAMICS AND OXYGEN TRANSPORT IN FULMINANT HEPATIC FAILURE

PHILLIP M. HARRISON, M.R.C.P., JULIA A. WENDON, M.R.C.P., ALEXANDER E.S. GIMSON, M.R.C.P., GRAEME J.M. ALEXANDER, M.R.C.P., AND ROGER WILLIAMS, M.D.

Abstract *Background.* When administered early after an overdose of acetaminophen, intravenous acetylcysteine prevents hepatic necrosis by replenishing reduced stores of glutathione. How acetylcysteine improves the survival of patients with established liver damage induced by acetaminophen, however, is unknown. This study was undertaken to determine whether the beneficial effect of acetylcysteine under such circumstances could be due to enhancement of oxygen delivery and consumption.

Methods. We studied the effect of acetylcysteine on systemic hemodynamics and oxygen transport in 12 patients with acetaminophen-induced fulminant hepatic failure and 8 patients with acute liver failure from other causes. The acetylcysteine was given in a dose of 150 mg per kilogram of body weight in 250 ml of 5 percent dextrose over a period of 15 minutes and then in a dose of 50 mg per kilogram in 500 ml of 5 percent dextrose over a period of 4 hours; measurements were made before treatment began and after 30 minutes of the regimen.

Results. In the patients with acetaminophen-induced liver failure, the infusion of acetylcysteine resulted in an increase in mean oxygen delivery from 856 to 975 ml per minute per square meter of body-surface area ($P = 0.0036$), due to an increase in the cardiac index from 5.6 to 6.7 liters per minute per square meter ($P = 0.0021$). Mean arterial pressure rose from 88 to 95 mm Hg ($P = 0.0054$) despite a decrease in systemic vascular resistance from 1296 to 1113 dyn · sec · cm^{-5} per square meter ($P = 0.027$). There was an increase in oxygen consumption from 127 to 184 ml per minute per square meter ($P = 0.0007$) associated with an increase in the oxygen-extraction ratio from 16 to 21 percent ($P = 0.022$). The effects in the patients with acute liver failure from other causes were similar.

Conclusions. The increase in oxygen delivery and consumption in response to acetylcysteine may account for its beneficial effect on survival in patients with fulminant hepatic failure induced by acetaminophen. (N Engl J Med 1991; 324:1852-7.)

Liver Transplantation

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Original Article | Free Access

Safety and efficacy of N-acetylcysteine in children with non-acetaminophen-induced acute liver failure

Christine Kortsalioudaki, Rachel M. Taylor, Paul Cheeseman, Sanjay Bansal, Giorgina Mieli-Vergani, Anil Dhawan

A retrospective review

King's College Hospital (1989-2004)

Group 1 (1989-1994) not treated with NAC (n = 59)

Group 2 (1995-2004) treated with NAC (n = 111)

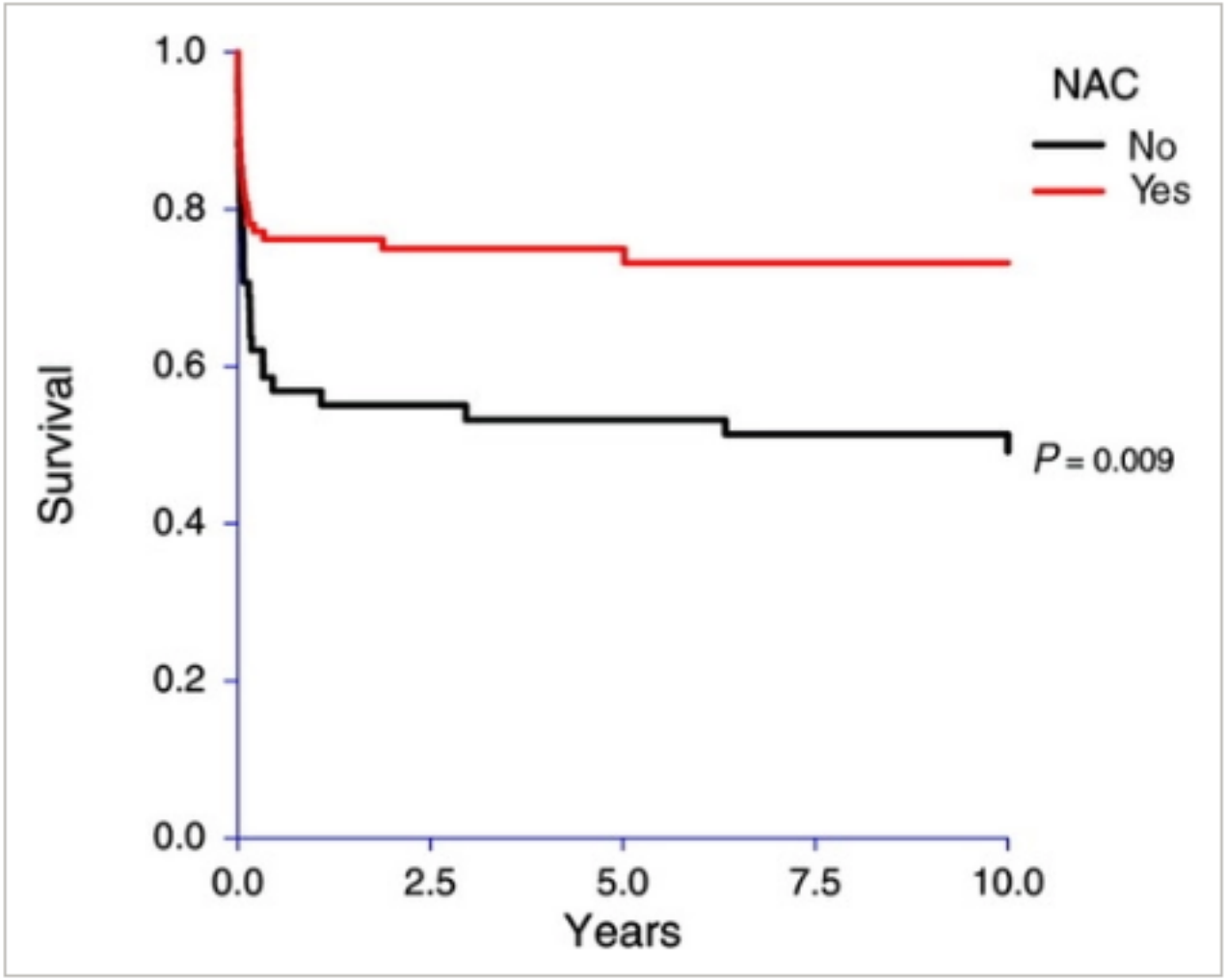

Figure 1

Open in figure viewer | PowerPoint

Actuarial survival of children who did not receive NAC (Group 1) compared to those who received NAC (Group 2).

Table 5. Outcome in Children Who Did Not Receive NAC (Group1) Compared to Those Who Received NAC (Group 2)

	Group 1 (n = 59)	Group 2 (n = 111)
Length of PICU stay (days) (median, range)	6 (1–58)	5 (1–68)
Length of hospital stay (days) (median, range)	25 (1–264)	19 (1–201) *
Alive with the native liver	13 (22%)	48 (43%) **
Died without LT	15 (25%)	21 (19%)
LT	32 (54%)	42 (38%)
Retransplantation	8 (26%)	6 (15%)
Died after LT	15 (39%)	8 (16%) ***

Abbreviation: PICU, pediatric intensive care unit.

* $P = 0.05$.

** $P = 0.005$.

*** $P = 0.02$.

Gastroenterology

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Gastroenterology. 2009 Sep;137(3):856-64, 864.e1. doi: 10.1053/j.gastro.2009.06.006. Epub 2009 Jun 12.

Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure.

Lee WM[1], Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, Davern TJ 2nd, Murray NG, McCashland T, Reisch JS, Robuck PR; Acute Liver Failure Study Group.

METHODS:

- In a prospective, double-blind trial

RESULTS:

- A total of 173 patients received NAC (n = 81) or placebo (n = 92). Overall survival at 3 weeks was 70% for patients given NAC and 66% for patients given placebo (1-sided P = .283). Transplant-free survival was significantly better for NAC patients (40%) than for those given placebo (27%; 1-sided P = .043). The benefits of transplant-free survival were confined to the 114 patients with coma grades I-II who received NAC (52% compared with 30% for placebo; 1-sided P = .010); transplant-free survival for the 59 patients with coma grades III-IV was 9% in those given NAC and 22% in those given placebo (1-sided P = .912). The transplantation rate was lower in the NAC group but was not significantly different between groups (32% vs 45%; P = .093). Intravenous NAC generally was well tolerated; only nausea and vomiting occurred significantly more frequently in the NAC group (14% vs 4%; P = .031).

CONCLUSIONS:

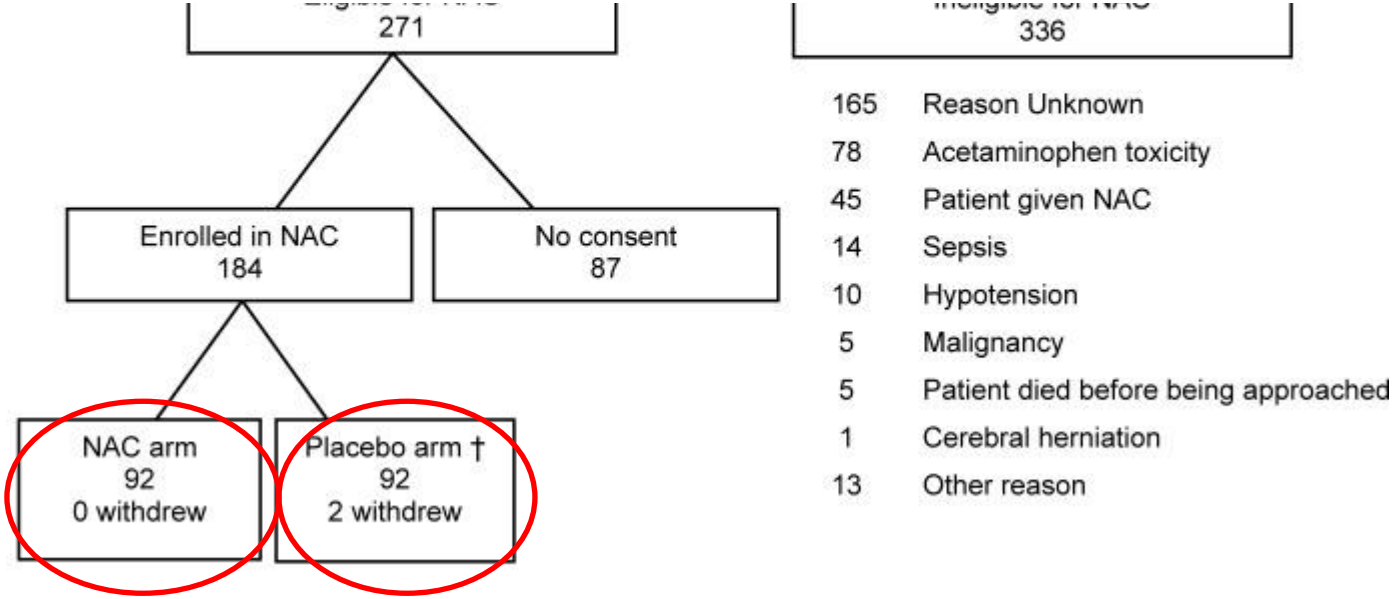
- Intravenous NAC improves transplant-free survival in patients with early stage non-acetaminophen-related acute liver failure. Patients with advanced coma grades do not benefit from NAC and typically require emergency liver transplantation.

HEPATOLOGY AASLD

Liver Failure/Cirrhosis/Portal Hypertension | Free Access

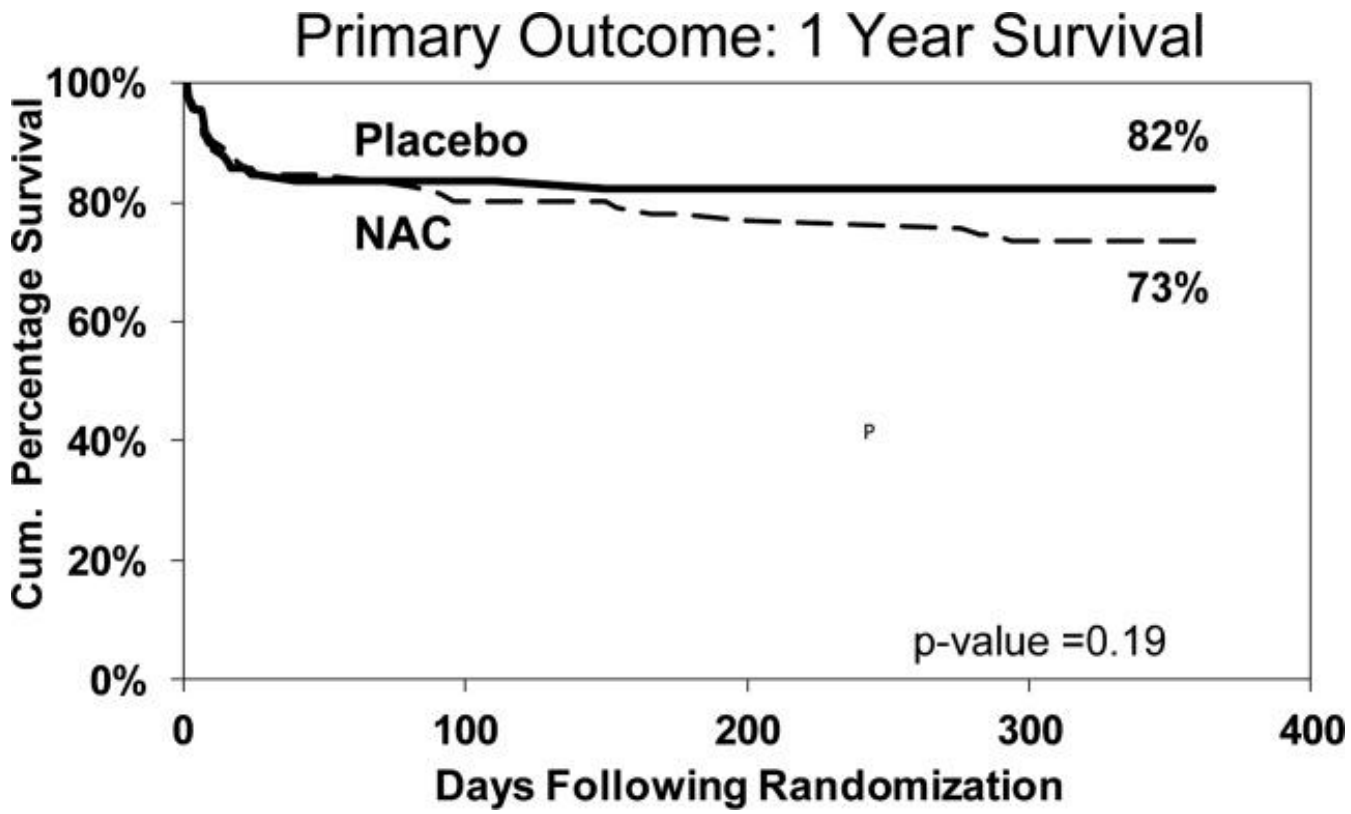
Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: A placebo-controlled clinical trial†‡

Robert H. Squires, Anil Dhawan, Estella Alonso, Michael R. Narkewicz, Benjamin L. Shneider, Norberto Rodriguez-Baez, Dominic Dell Olio, Saul Karpen, John Bucuvalas ... See all authors



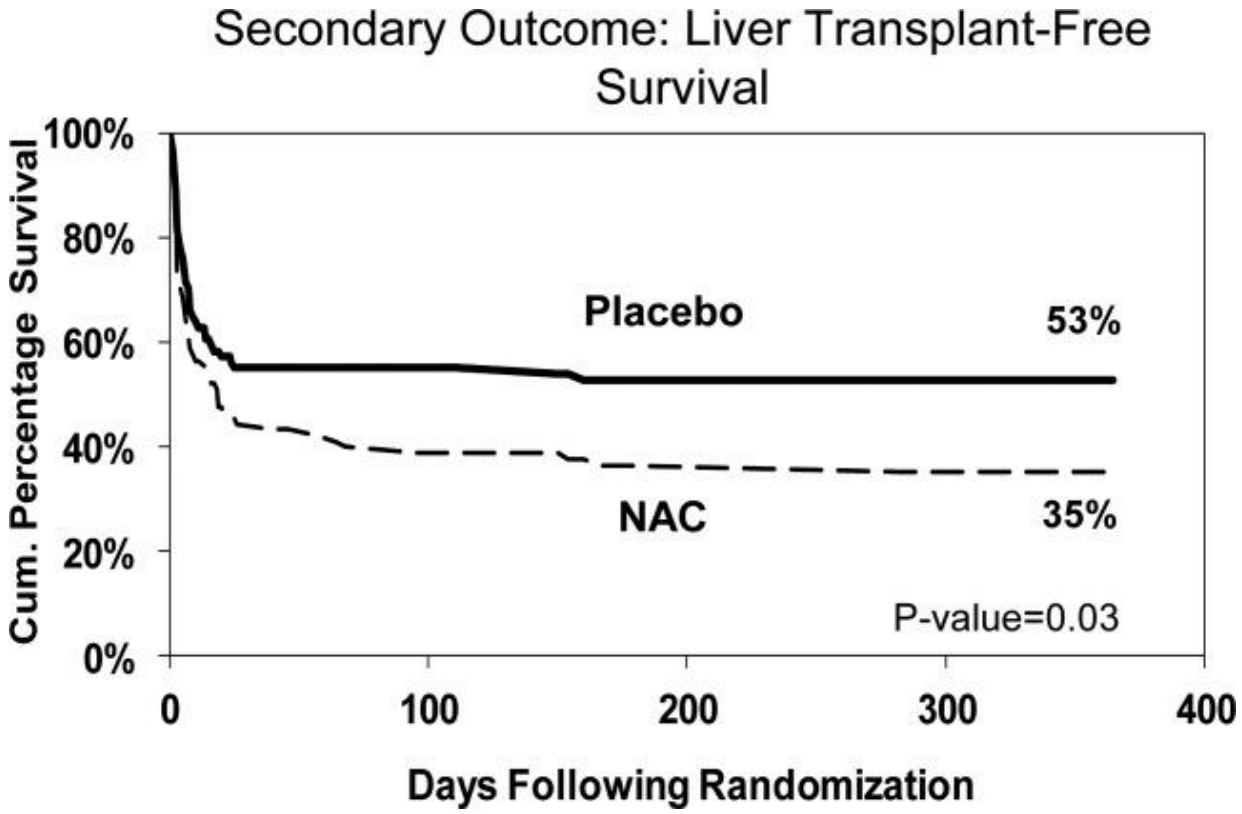
† One participant was randomized to placebo arm but received treatment.

Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: A placebo-controlled clinical trial



Hepatology, Volume: 57, Issue: 4, Pages: 1542-1549, First published: 10 August 2012, DOI: (10.1002/hep.26001)

Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: A placebo-controlled clinical trial



Hepatology, Volume: 57, Issue: 4, Pages: 1542-1549, First published: 10 August 2012, DOI: (10.1002/hep.26001)

Liver INTERNATIONAL

Cirrhosis and Liver Failure

Effects of *N*-acetylcysteine on cytokines in non-acetaminophen acute liver failure: potential mechanism of improvement in transplant-free survival

R. Todd Stravitz ✉, Arun J. Sanyal, Joan Reisch, Jasmohan S. Bajaj, Farid Mirshahi, Jenfeng Cheng, William M. Lee, The Acute Liver Failure Study Group

Liver Int. 2013 Oct;33(9):1324-31. doi: 10.1111/liv.12214. Epub 2013 Jun 19.

Effects of N-acetylcysteine on cytokines in non-acetaminophen acute liver failure: potential mechanism of improvement in transplant-free survival.

Stravitz RT[1], Sanyal AJ, Reisch J, Bajaj JS, Mirshahi F, Cheng J, Lee WM; Acute Liver Failure Study Group.

Author information

Abstract

BACKGROUND: N-Acetylcysteine (NAC) improves transplant-free survival in patients with non-acetaminophen acute liver failure (ALF) when administered in early stages of hepatic encephalopathy. The mechanisms of this benefit are unknown.

AIM: To determine whether NAC improves transplant-free survival in ALF by ameliorating the surge of pro-inflammatory cytokines.

METHODS: Serum samples were obtained from 78 participants of the randomized, ALF Study Group NAC Trial with grade 1 or 2 hepatic encephalopathy on randomization. Concentrations of ten cytokines, chosen to represent a wide array of inflammatory responses, were determined by multiplex enzyme-linked immunosorbent assay ELISA.

RESULTS: In univariate analysis, predictors of transplant-free survival included NAC administration ($P = 0.012$), admission bilirubin ($P = 0.003$), international normalized ratio INR ($P = 0.0002$), grade 1 vs. grade 2 encephalopathy ($P = 0.006$) and lower admission interleukin (IL)-17 concentrations ($P = 0.011$). IL-17 levels were higher in patients with grade 2 vs. grade 1 encephalopathy on randomization ($P = 0.007$) and in those who progressed to grade 3 or grade 4 encephalopathy over the following 7 days ($P \leq 0.01$). Stepwise multivariate logistic regression analysis identified only NAC administration and lower IL-17 concentrations as independent predictors of transplant-free survival. In patients with detectable IL-17 concentrations on admission, 78% of those who received NAC vs. 44% of those who received placebo had undetectable levels by day 3-5 ($P = 0.042$), and the mean decrease in IL-17 concentrations between admission and late samples was significantly greater in patients who received NAC vs. placebo ($P = 0.045$).

CONCLUSIONS: N-acetylcysteine (NAC) may improve transplant-free survival in patients with non-acetaminophen ALF by ameliorating the production of IL-17, which is associated with progression of hepatic encephalopathy and poor outcome.

DIGESTIVE DISEASES AND SCIENCES
Formerly Published as The American Journal of Digestive Diseases

Dig Dis Sci. 2013 May;58(5):1397-402. doi: 10.1007/s10620-012-2512-x. Epub 2013 Jan 17.

Improvements in hepatic serological biomarkers are associated with clinical benefit of intravenous N-acetylcysteine in early stage non-acetaminophen acute liver failure.

Singh S[1], Hynan LS, Lee WM; Acute Liver Failure Study Group.

Author information

Abstract

BACKGROUND: N-acetylcysteine (NAC) improves transplant-free survival in early coma grade (I-II) patients with non-acetaminophen induced acute liver failure (ALF). We determined whether the clinical benefit was associated with improvements in hepatic function.

METHODS: In a prospective, double blind trial, 173 ALF patients without evidence of acetaminophen overdose were stratified by coma grade (I-II vs. III-IV) and randomly assigned to receive either intravenous NAC or dextrose (placebo) for 72 h, resulting in four patient groups. INR, ALT, bilirubin, creatinine, and AST obtained on admission (day 1) and subsequent days (days 2-4) were used for secondary analysis performed by fitting longitudinal logistic regression models to predict death or transplantation or transplantation alone.

RESULTS: Treatment group and day of study in models including bilirubin or ALT were predictors of transplantation or death (maximum $p < 0.03$). Those patients with early coma grade who were treated with NAC showed significant improvement in bilirubin and ALT levels when compared to the other three groups (maximum $p < 0.02$ for NAC 1-2 vs. the 3 other treatments) when predicting death or transplantation. Treatment group, day of study, and bilirubin were predictors of transplantation (maximum $p < 0.03$) in ALF patients.

CONCLUSION: The decreased risk of transplantation or death or of transplantation alone with intravenous NAC in early coma grade patients with non-acetaminophen induced ALF was reflected in improvement in parameters related to hepatocyte necrosis and bile excretion including ALT and bilirubin, but not in INR, creatinine, or AST. Hepatic recovery appears hastened by NAC as measured by several important lab values.

Clinics and Research in Hepatology and Gastroenterology
Volume 39, Issue 5, October 2015, Pages 594-599

Original article

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

Jinhua Hu [a], Qizhi Zhang [b], Xingye Ren [b], Ziqin Sun [a], Qizhen Quan [a]
Show more

Study or Subgroup	NAC Events	NAC Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kortsalioudaki 2008	90	111	44	59	19.9%	1.46 [0.69, 3.11]
Lee(2009)	57	81	61	92	30.9%	1.21 [0.63, 2.30]
Mumtaz 2009	22	47	12	44	12.0%	2.35 [0.98, 5.64]
Squires 2013	67	92	74	90	37.2%	0.58 [0.29, 1.18]
Total (95% CI)		**331**		**285**	100.0%	**1.16 [0.81, 1.67]**
Total events	236		191			

Heterogeneity: Chi² = 6.63, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 0.81 (P = 0.42)

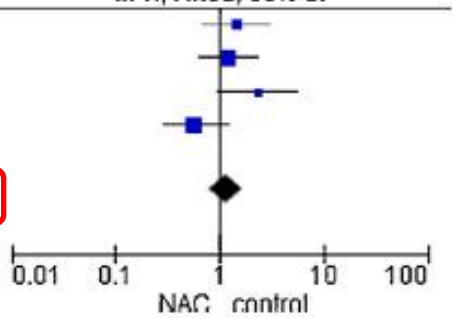


Figure 2 The forest plot for overall survival in NAC group and control group.

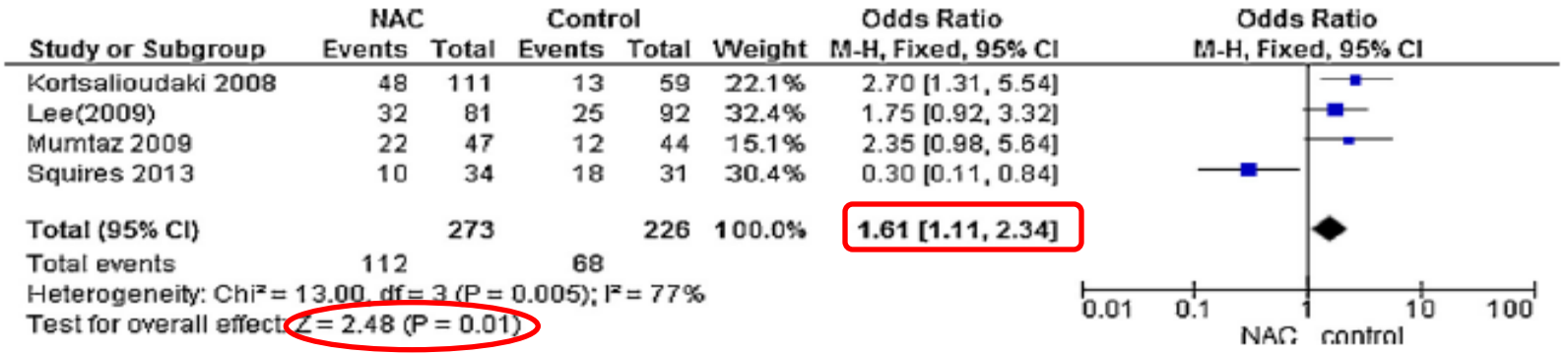


Figure 3 The forest plot for transplant-free survival in NAC group and control group.

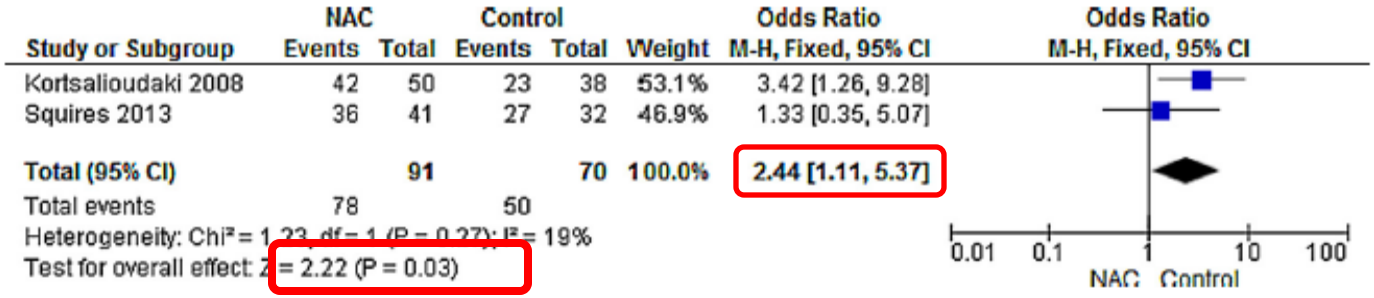


Figure 4 The forest plot for post-transplantation survival in NAC group and control group.

Clinical Drug Investigation
May 2017, Volume 37, Issue 5, pp 473–482 | Cite as

Effect of *N*-Acetylcysteine on Mortality and Liver Transplantation Rate in Non-Acetaminophen-Induced Acute Liver Failure: A Multicenter Study

Authors | Authors and affiliations

Samar K. Darweesh, Mona F. Ibrahim, Mahmoud A. El-Tahawy

Characteristic	NAC	Control group	*p* value
Smoking	42 (50)	32 (46.7)	0.796
Drug abuse	5 (6.7)	6 (10.0)	1.0
Co-morbidity	40 (46.7)	37 (53.3)	0.606
Encephalopathy at admission	24 (28.2)	25 (35.7)	1.0
Encephalopathy grade			
0	61 (71.7)	45 (64.2)	0.7
I–II	20 (23.5)	19 (27.1)	
III–IV	4 (4.7)	6 (8.5)	
During hospital course after NAC			
Encephalopathy during course	28 (33.3)	44 (63.3)	0.02
Hospital stay (days)	10.1 ± 3.89	28.0 ± 5.32	<0.001
ICU admission	28 (33.3)	47 (66.7)	0.01
Bleeding	20 (23.3)	47 (66.7)	<0.01
RFT during course (normal)	56 (66.7)	16 (26.7)	0.002
Electrolytes during course (normal)	65 (76.7)	16 (26.7)	<0.01
Hb during course (normal)	56 (66.7)	32 (46.7)	0.118
WBCs during course (normal)	65 (76.7)	40(56.7)	0.1
Platelets during course (normal)	56 (66.7)	44 (63.3)	0.787

Table 3 Outcome of the study in the two groups

Outcome	*N*-acetyl cysteine group	Control group	*p* value
Recovered	82 (96.4)	17 (23.3)	<0.01
Died	1 (3.3)	16 (23.3)	
Liver transplantation	2 (6.7)	37 (53.3)	
Total	85	70	

Values are expressed as *N* (%)

CONCLUSION

- NAC is safe for NAI-ALF.
- In aldult, NAC improves transplant-free survival with early stage, improvements in all parameters of liver injury.
- In children, NAC did not improve 1-year survival in non-APAP PALF. 1-year LTx-free survival was significantly lower with NAC, < 2 years old.
- Don’t determine the optimal dose and duration of NAC therapy.
- ESPGHAN and NASPGHAN 2017 , not recomment the use of NAC in children with non-APAP ALF.

Lutfi R[1], Abulebda K (2017), “” Intensive Care Management of Pediatric Acute Liver Failure””. *J Pediatr Gastroenterol Nutr*, 64(5), pp 660-670.