Clinical Research in Practice: The Journal of Team Hippocrates

Volume 2 | Issue 2 Article 2

2016

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Recommended Citation
Robinson D. Salvage therapy for non-acetaminophen-induced acute liver failure includes N-acetylcysteine. *Clin. Res. Pract.* 2016 July 19;2(2):eP1103. doi: 10.22237/crp/1469036118

Clinical Research in Practice
The Journal of Team Hippocrates
VOL 2 ISS 2 / eP1103 / JULY 20, 2016

Salvage therapy for non-acetaminophen-induced acute liver failure includes N-acetylcysteine

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ABSTRACT A critical appraisal and clinical application of Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology.* 2009;137(3):856-864. doi: 10.1053/j.gastro.2009.06.006

Keywords: N-acetylcysteine, acute liver failure, non-acetaminophen-induced

Clinical Context

C.J. was a 39-year-old female with a fifteen-year history of depression who presented to the emergency department (ED) with acute liver failure, acute renal failure, and rhabdomyolysis from a suspected toxic ingestion. Her family found her, unresponsive, lying in a pool of vomit containing 25 unknown pills. Of note, she had recently been prescribed 65 tablets of Oxycodone for pain control after undergoing a video-assisted thoracoscopic surgery earlier that week. En route to the ED, she experienced multiple hypotensive episodes, with 70/55 mmHg being the lowest blood pressure recorded. On arrival at the ED, the patient was in acute liver failure, with liver function tests that peaked at an ALT of 8,329 IU/L and an AST of 5,762 IU/L. In addition, she had an acute kidney injury with a maximum creatinine of 4.2 mg/dL and rhabdomyolysis with a CPK of 2,328 IU/L. She was severely obtunded. Her INR was 1.7 and serum acetaminophen level was undetectable. N-acetylcysteine (NAC) was started as an adjunctive therapy for non-acetaminophen-induced acute liver failure with ischemic liver, which puts the patient at greater risk for mortality. The patient had a hepatic encephalopathy coma grade of III.

Clinical Question

Does administration of N-acetylcysteine provide any mortality benefit to adults in non-acetaminophen-induced acute liver failure (NAI-ALF)?

Research Article

Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology.* 2009;137(3):856-864. doi: 10.1053/j.gastro.2009.06.006 [1]

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ISSN: 2379-4550
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Clinical Research in Practice
The Journal of Team Hippocrates
VOL 2 ISS 2 / ePI103 / JULY 20, 2016

Literature Review

This article was chosen for review after searching the PubMED database for articles that contained the keywords "non-acetaminophen-induced acute liver failure" and "N-acetylcysteine". 20 articles were found. Studies that did not address the clinical question were excluded. A retrospective study by Kortsalioudaki[2] showed that NAC in NAI-ALF was associated with a shorter length of hospital stay by 6 days (*P*=0.05), higher incidence of native liver recovery without transplantation (43% compared to 22%, *P*=0.005), and better survival after transplantation (84% compared to 61%, *P*=0.02).

A prospective study in 2009 by Mumatz et al. furthered this by showing NAC administration was effective in reducing mortality for NAI-ALF. The survival in the supportive care group was 27% versus 47% in the NAC group.[3] Devlin et al. proposed a mechanism by which NAC could provide benefit in NAI-ALF, reporting that NAC is thought to help the resultant tissue hypoxia through its antioxidant and vasodilating effects.[4]

In 2015, Jinhua et al. published a meta-analysis analyzing four major studies on the topic. They performed a similar literature review as described above, and found 15 unique studies; they excluded two reviews and nine non-relevant studies from their analysis.[5] The largest study with the most statistical weight in the meta-analysis showed results consistent with the meta-analysis's conclusions, and was chosen for this clinical appraisal. It was also the only double-blinded randomized controlled trial available on the subject. Lee and his co-authors' double-blinded randomized controlled trial had the largest sample size (*N*=173) of all relevant studies, and thoroughly addresses the clinical question, making it the most appropriate candidate for this critical appraisal. This critical appraisal therefore looks to evaluate the evidence supporting the efficacy of NAC administration for patients in NAI-ALF.

Critical Appraisal

This was a double-blinded randomized controlled trial by with sample size *N*=173. The U.S. Acute Liver Failure Study Group conducted this study from 1998-2006 at 24 participating sites around the United States. Inclusion criteria included age greater than 18 years; evidence of acute liver failure: INR of 1.5 or greater along with any amount of encephalopathy in a patient without preexisting cirrhosis; and a length of illness less than 24 weeks. This is consistent with standard acute liver failure diagnostic criteria and represents patient populations at any non-pediatric hospital in the United States.[6] Eligible participants were stratified via degree of hepatic encephalopathy (HE) coma grades I-II (mild-moderate) and III-IV (severe), and received either IV NAC or placebo (5% dextrose) for a total duration of 72 hours.[1] HE coma grades are determined using the West Haven Grading System. Patients were excluded for ALF with suspected acetaminophen overdose; previous treatment with NAC; liver failure caused by pregnancy or cancer; and hepatic ischemia.

Randomization was stratified by site and coma grade with a blocking factor of four.[7] The randomization list was prepared by an un-blinded statistician, adding a possible source of selection bias. Additionally, methodology on how randomization was performed is not explicitly stated, introducing possible selection bias. Groups were similar in demographics, with only two parameters being significantly different between groups: more females and a longer median onset of jaundice to coma in the placebo group. The investigators attempted an intention to treat analysis: nine patients were excluded, approximately five percent. This is a small enough number of cases that it does not affect the overall analysis. The standard of care was provided for both treatment and placebo groups.

The primary outcome was overall number of patients surviving at three weeks after study admission. This was a reasonable primary outcome. The NCT registration (NCT00004467) confirms this outcome measure. There was no significant difference in primary outcome between patients receiving NAC compared to placebo, 70% vs. 66% (*P*=0.28). However, transplant-free survival at 21 days was significant for coma grades I-II, 52% vs. 30% (*P*=0.01). Transplant-free survival was not significant for coma grades III-IV, 9% vs. 22% (*P*=0.18). This demonstrates the importance of coma grading at admission.

Subgroup analyses were used for most outcome conclusions, which is a limitation of this study. The authors make claims about differences between coma grades I-II versus III-IV, but in NCT00004467 this differentiation is not mentioned, making any conclusion speculative with uncertain validity. The way the authors report results is misleading. However, this is the best available evidence for this patient.

ISSN: 2379-4550
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VOL 2 ISS 2 / eP1103 / JULY 20, 2016

The number of trial participants with coma grades I-II was quite larger than those with coma grades III-IV: *n*=114 vs. *n*=57. The authors concede that many more patients that may have been in the coma grade III-IV group met exclusion criteria than those with early coma grades. This makes the apparent, although not statistically significant, overall survival improvement from NAC administration subjective to overrepresentation of early coma grade and is a shortfall of the study. With the data from Table 2 of the reviewed article, the number needed to treat for overall survival and transplant-free survival were 24 and 8, respectively.

The study design called for 80% power to detect a 20% difference in overall survival at three weeks. The study was powered to detect this difference. However, the actual effect size was 4%. Because the investigators overestimated the effect size, this was an underpowered study.

The medication was well tolerated overall. The only important adverse effect was an increase of nausea and vomiting in the treatment group (14% vs. 4%, NNH 10, *p*=0.031). This did not cause any drop-outs in the trial.

This single randomized control trial falls into the 1b level of evidence according to the Oxford Centre for Evidence-Based Medicine. Sub-group analysis provided the transplant-free survival data that reached statistical significance for coma grade I-II hepatic encephalopathy, making the clinical benefit of using NAC in NAI-ALF difficult to determine definitively. While transplant-free survival in coma grades I-II was improved, overall survival was not. Multiple studies on the topic have failed to show an absolute survival benefit with the use of NAC in NAI-ALF, yet it has been shown to potentially increase survival in select subgroups. Coma grade at admission and transplantation availability appear to be the most important prognostic indicators. It is a medication with few adverse effects, and due to the lack of alternative therapies aside from transplantation, it is reasonable to conclude that the use of NAC in NAI-ALF can provide transplant-free survival benefit when used in the care of liver failure patients with coma grades I-II hepatic encephalopathy.

Clinical Application

Our patient presented with NAI-ALF, most likely from liver shock resulting from severe ischemia after a toxic ingestion. Therefore, she would not have been an eligible subject in the trial. However, she was severely ill and the treatment team thought that some type of therapy was appropriate. While the results failed to reach statistical adequacy, a 4% reduction in mortality was felt to be a clinically meaningful outcome. Since there was relatively little risk of harm from the use of this medication when weighed against the mortality benefit, NAC therapy was administered. The patient responded well and eventually made a full recovery. Due to the ambiguous results and subgroup analyses composing most of this study's conclusions, treatment decisions remain largely a clinical judgment. For future patients presenting with NAI-ALF, I would consider using NAC as an adjunctive treatment due to its minimal side effect profile and possible benefit for survival and transplant-free survival. In situations of ALF of unknown origin, it is a potentially helpful medication and should be considered for use. More studies analyzing specific subgroups are needed to elucidate the definitive benefits of NAC.

Lessons:

1.) The therapeutic effects of N-acetylcysteine need more research. Meanwhile, clinical judgment should guide decision making for critically ill patients. It is important to remember the distinction between statistically significant outcomes and clinically meaningful outcomes, because it plays a large part in offering therapy to patients.
2.) NAI-ALF has a very high mortality rate, and definitive treatments other than liver transplantation are not well described.
3.) The use of N-acetylcysteine in NAI-ALF has questionable benefits, but little to no harm, and can be safely used as an adjunctive therapy in ALF.

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