STUDY ON THE EFFECT OF NAC IV IN ACUTE EPISODE OF LIVER DYSFUNCTIONS

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Summary

Objectives: Evaluate the effectives and safety of IV NAC in acute episode of liver dysfunctions patient treated in Huunghi Viet Tiep Hospital.

Material and methods: 31 patients treated in Tropical Diseases Department of Huunghi Viet Tiep Hospital who had acute episode of liver dysfunctions from April 15th to July 15th.

Before-after study, compare the results before and after treatment. Beside the original treatment followed the hospital's guideline, selected patients were received N-acetylcystein IV 100 mg/kg/24h in glucose 5% for 7 days. Patients had health check every day and liver function test was performed before treatment (D0) and on the 3rd and 7th day of treatment or the discharged date (D3 and D7).

Results: After 7 days of treatment, the average value of ALT, AST, and GGT reduced from 626.1 ± 234.8 to 322.5 ± 121.1 (about 50%), from 495.4 ± 178.1 to 127.2 ± 76.5 (about 70%), and from 292.1 ± 88.5 to 227.9 ± 57.4, prospectively. There were 22 patients having high bilirubin value, and after 7 days of treatment, the average reduced 22%. 80.6% patients improved, the average hospital length of stay is 8.68 ± 2.97 days, no patient need for transplant. There was no severe adverse reaction or anaphylactic shock occurred.

Conclusion: NAC IV was safe and effective in preventing the further progression of liver failure..

Keywords: *N-Acetylcystein (NAC), Acute liver failure (ALF), Non-acetaminophen induced acute liver failure (NAI-ALF), acute episode of liver dysfunctions.*

INTRODUCTION

Acute liver failure (ALF) is relatively rare, but it affects children and adults across the world and confers significant morbidity and mortality and demand for liver transplant.This is the development of severe acute episode of liver dysfunction which is characterized by hepatic encephalopathy and high blood transaminase level, coagulopathy of liver aetiology (INR ≥ 1.5) in patients without underlying chronic liver disease1. The Onset of less than 26 weeks is often used to distinguish between acute and chronic liver failure. Viral hepatitis and medicines caused hepatitis (mostly due to acetaminophen) are the most common causes of ALF all over the world[2,3].

The treatment of ALF mainly focuses on management of cerebral enema, symptoms treatment and other supportive methods until the recovery of live function. It is necessary to establish a solution aimed to protect liver tissue and prevent the progress of liver tissue damage. According to many studies, etiologies causing ALF directly deplete glutathion - a necessary chemical for liver function[4,6]. Increasing the intracellular glutathione levelis demonstrated play an important role in protecting liver tissue from the toxical agents[4,9].

N-acetylcystein (NAC) has been in widespread use since the 1970s for the treatment of AI-ALF because it is the supplemental L-cystein source which is necessary for intracellular glutathione synthesis, this indication is approved in all over the world as the only choice of acetaminophen over dose treatment.

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Early use of NAC in the NAI-ALF has been also proved that it is effective in decreasing liver enzymes levels, protecting liver tissue and reducing the risk of liver transplant and mortality rate due to acute liver failure[10]. NAC can be administered by both oral route and intravenous (IV) route. However, studies indicated that the oral route is less absorbable in the case of NAI-ALF, especially in patients with a lot of nausea and vomitting[11,13].

In Vietnam, NAC was studied and used in AI-ALF14, however, no study reseaches its use in NAI-ALF, especially IV NAC. Therefore, we conduct this study to evaluate the effects and safety of IV NAC in NAI-ALF patients with following purposes:

(1). Effect of liver protection based on evaluating liver function test in NAI-ALF patients treated with IV NAC.

(2). Observe the length of hospital stay of NAI-ALF treated with IV.

(3). Evaluate the adverse reactions of IV NAC in NAI-ALF patients.

SUBJECTS AND METHODS

We conducted the before-after study with IV NAC in the patient diagnosed with NAI-ALF in Tropical Deseases Department of Huunghi Viet Tiep Hospital in Hai Phong from April 15th to July 15th, 2022. The Reseach was discussed and approved by Huunghi Viet Tiep Hospital Scientific Committee.

The ALF was diagnosed based on the European Association for the Study of the Liver clinical practice guidelines on the management of acute liver failure[1]. The research elimated patients not agree to participate in, patients less than 18 years old, pregnant and breast feeding patients. Patients with historically allergy to NAC, asthma, oliguria or anuria, and risk of fluid overload were also elimated from this research.

Patients were carefully examinated, and done liver function tests at the time of hospital admission and ALF diagnosis. After that, beside causes of desease treatment following hospital's protocol and guidelines, selected patients were received NAC (BFS-Depara, CPC1) with the dose of 100 mg/kg/24h (diluted in Glucose 5% solution, instravenous infusion) in 7 days or until discharging[15].

Patients were done health check every day and monitored the adverse reactions can appear during treatment period. Liver function tests were conducted on the third and the seventh day of treatment (or the discharging day if the length of hospital stay is less than 7 days). Evaluate the recovery of liver function based on these criteria: Prothrombin (PT), Billirubin total, liver enzymes. Length of hospital stay was calculated from the admission date to discharging date or death. Record the cases have to move to ICU or death. Observe the adverse reaction related to administration of IV NAC.

We used Paired T-Test to examinate the average values before and after treatment and create the figure with the graphpad prism[7]. The comparable results are considerd significantly different if P values are less than 0.05.

RESULTS

Characteristics of research subjects

After elimination of patients who did notcomply with research's criteria, 31 NAI-ALF patients were selected for the research.

Age, gender and comorbidity: The mean age of the patients is 51.5 ± 15.08 years, most of those are more than 50 years old (about 61.3%), gender rate is approximately 1/1. Retirer and freelancer dominated more than 80%. 35% of patients consumpt alcohol regularly. 61.3% of the patients had comorbidity, more than 50% of those are hypertension and diabetes.

Etiologies: 54.3% of the cases in this research were caused by hepatitis virus, mostly was Hepatitis B virus (HBV). Sepsis was the second common cause, dominated 11.4%.

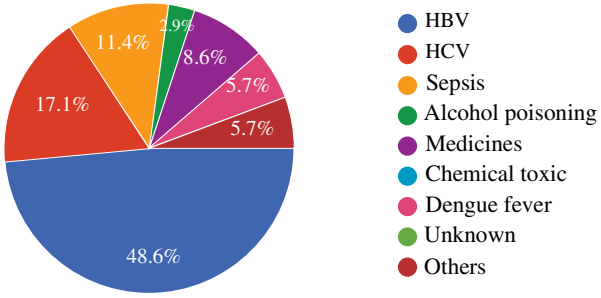


Figure 1. Causes of acute liver failure in the research

Clinical symptoms: More than 90% of patients had fatigue, and lost appitite. Right flank pain and jaundiceappeared at 30 - 40% of patients. Other symptoms such as enema, hemorrhage occurred at approximate 10% of cases.

Liver function tests: All the patients showed abnormal results. The ALT (626.1 ± 234.8 UI/L), AST (495.4 ± 178.1 UI/L), GGT (292.1 ± 88.5 UI/L), and bilirubin total (120.4 ± 31.2 micromol/L) increased highly compared to normal liver function tests, which reflected the acute liver failure.

Comparison of before and after treatment results

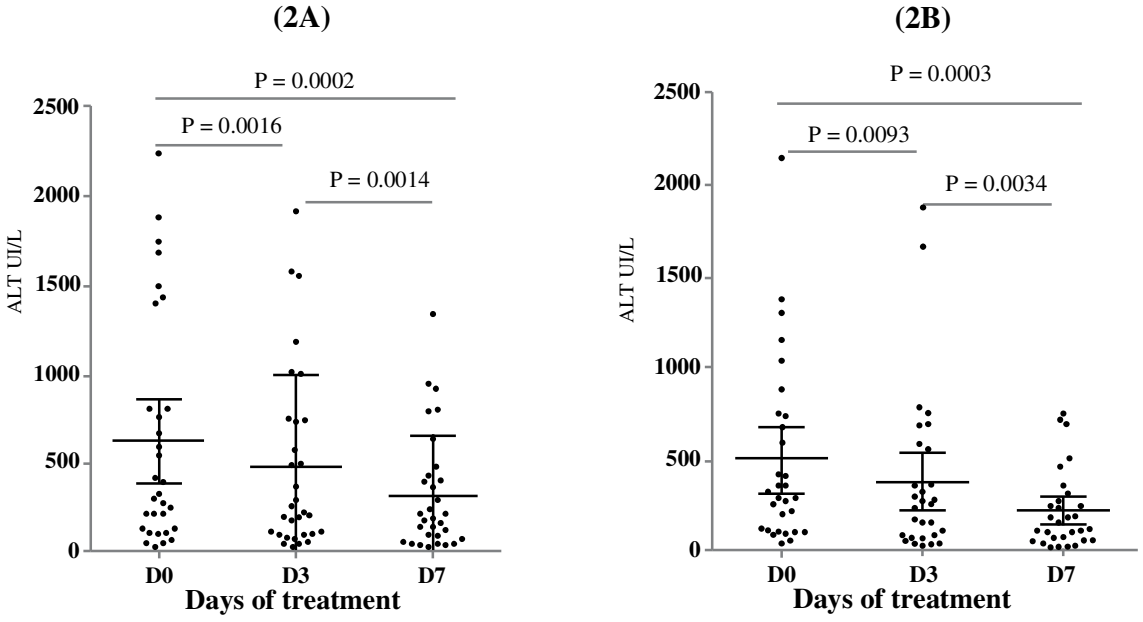
Clinical syptoms: 80.6% have clinical syptoms improved significantly after 7 days of treatment. There were 3 cases occurred sepsis shock and have to be moved to ICU, dominated 9.7%.

Liver function tests:

Table 1. Comparison of liver function test values before and after treatment with IV NAC

	D0	D3			D7		
	Mean ± SD	Mean ± SD	Percentage decrease (%)	P	Mean ± SD	Percentage decrease (%)	P
ALT	626.1 ± 234.8	477.0 ± 188.7	23.8%	< 0.01	322.5 ± 121.1	48.5%	< 0.001
AST	495.4 ± 178.1	377.5 ± 159.8	23.77%	< 0.01	127.2 ± 76.5	74.3%	< 0.001
GGT	292.1 ± 88.5	267.1 ± 76.2	8.5%	< 0.05	227.9 ± 5.4	22%	< 0.01
Billtp	120.4 ± 31.2	114.9 ± 41.5	4.6%	> 0.05	95.0 ± 43.5	21.13%	< 0.01

Liver enzymes and bilirubin total significantly decreased after 3 days of treatment with IV NAC, and continue decreasing statical significantly after 7 days, in combination with those before treatment ($p < 0.01$) (Table 1, Figure 2).



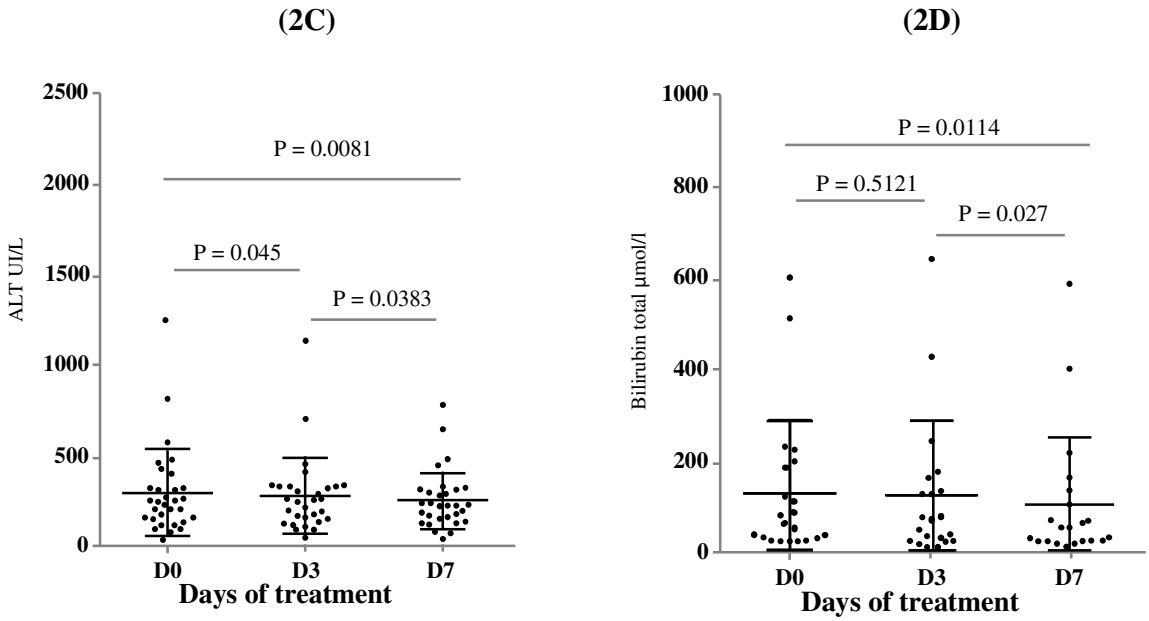


Figure 2. Liver enzyme (ALT, AST, GGT) and bilirubin total level before (D0), the third day (D3), and the 7th day (D7) of treatment with IV NAC

Length of hospital stay and motordity rate: The Mean of Length of hospital stay was 8,68 ± 2.97 days, of those the shortest time was 5 days and the longest time was 17 days. There was no mortality or demand for liver transplant.

Monitoring advert reactions

In this study, we did not receive any anaphylaxis, allergic reaction or any severe adverse reactions. There were 5 cases (16.13%) appeared mild reactions considered relating to IV NAC: 3 case had nausea, vomiting, 1 case had hadache and insomnia, the other appeared fatigue. There were two patients who occurred continuously vomit at the second day of treatment, the symptoms stopped after discontinuing treatment with IV NAC and these patients were eliminated from the research. The other cases, the reaction appeared on the third or the fourth day of treatment and do not have any signals of more complicated, all the symptoms disappeared after stopping the medication.

DISCUSSION

In this research, we monitored 31 patients diagnosed with NAI-ALF and received early treatment with IV NAC, we found that the clinical symptoms and liver function tests were significantly improved after 3-day treatment and 7-day treatment. Patients were discharged within a short time; the mean of hospital stay duration was 8.68 ± 2.97 days. There was no mortality and demand for liver transplant.

Many previous prospective studies and randomized clinical trials also indicated that NAC plays an important role in the treatment of NAI-ALF[16]. According to the study of Khalid Mumtazand partners, patients in the control group (not treated with NAC) had higher risk of PT lasting more than 50 seconds and higher risk of jaundice and hepatic encephalopathy than those in the treatment group[17]. The length of hospital stay was also shorter in the NAC treated group in comparision with the NAC non treated group. In the severe septic shock patients, early treatment with NAC showed great improvement in patient's arterial blood gas levels, shortened the duration of ventilation and length of ICU stay. A double-blind randomized controlled trial of William M Leeand partners supported that treatment with NAC is effective inreducing mortality rate and risk of liver transplant in NAI-ALF patients.

Even though NAI-ALF is contributed by multiple etiologies, the mechanism of acute live dysfunction and failure are believed to result directly from

oxidative stress induced glutathione depletion[10]. Glutathione plays a crutial role in neutralization of free radicals produced by phase I liver metabolism of chemical toxins and directly deal with the causes of oxidative stress, that helps to protect liver tissues, reduce apotopsis and prevent the desease progress]. Therefore, increasing glutathione is necessary for liver tissue protection and recovery. The studies in human demonstrated that glutathione can not be transported directly through tissue membrane to the intracellular. Out side the cells, glutathione was degradated into L-glutamic, L-cystein and glycine, which are transported into the intracellular where they react to each other under the catalyzation of enzymes to synthesis intracellular glutathione. Of the ingredients of glutathione synthesis, cysteine availability is the rate-limiting step in the de novo production of glutathione. NAC which has been considered as the best effective and safest source of L-cystein helps to increase significantly intracellular Glutathione. As a consequence, NAC is suitable medication for ALF[10].

According to the safety, NAC is a well tolerated medicine and less adverse effects even with the intravenous administration. The adverse reactions reported include allergic reaction (bronchospasm, and rash), arrhythmia and other reactions (dizzy, and enema). Our research aslo showed that there were not any severe adverse effects with the treatment of IV NAC. Besides, by using optimal dose of NAC followed by recommendation, it did not harm tissue liver under the condition of acute liver failure.

CONCLUSION

In conclusion, our research on 31 none-acetaminophen induced acute liver failure patients treated in Tropical Deseases Department of Huunghi Viet Tiep Hospital indicated that IV NAC is effective in liver tissues protection and recovery, reducing length of hospital stay. Our data also supported for its safety in those patients.

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