N-acetyl Cysteine Therapy as Adjunctive Therapy for Treatment of Acute Hepatitis A

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Background and study aim: Hepatitis A is an acute, usually mild and self-limiting disease of the liver. We aim to assess the effect of oral N-acetyl cysteine compared with placebo on length of hospital stay in adult patients who were admitted to hospital with acute hepatitis A which might cause earlier resolution of hepatitis.
Subjects and Methods: 40 patients were diagnosed as acute hepatitis A and divided into two groups, the first one involved 20 patients who received oral N-acetyl cysteine and supportive treatment, and the second one involved also 20 patients but they received placebo and supportive treatment. We measured liver function test (LFT), kidney profile (KP), complete blood count (CBC), blood glucose, C-reactive protein (CRP) and coagulation profiles on the day of presentation, and every other day till the day of discharge from the hospital. Serological tests were done for HAV Immunoglobulin M (IgM), HBsAg, HBcIgM, antibody to Hepatitis C virus.
Results: The mean length of hospital stay in the NAC group was 13.2 days compared with 14.3 days in the placebo group. Length of hospital stay differed significantly between groups. The mean time of reliving symptoms at presentation was 3.6 days in the NAC group and 4.4 days in the placebo group. The mean time of reliving symptoms at presentation was significantly lower in NAC group than in placebo group.
Conclusion: use of oral NAC as adjunctive therapy for treatment of acute hepatitis A was associated with a shorter length of hospital stay and the use of NAC was safe in these patients.

INTRODUCTION

Hepatitis A is an acute, usually mild and self-limiting disease of the liver caused by the hepatitis A virus (HAV) **[1]**. The disease varies in clinical severity from a mild illness lasting 1-2 weeks to a severely disabling disease lasting several months. Most patients make a complete recovery **[2]**. HAV hepatitis does not progress to chronic liver disease and there is no chronic carrier state. On rare occasions the disease may be very severe, with fulminant hepatitis, liver coma and death [2]. Severity of illness is strongly age dependent. Young children who are infected with hepatitis A typically have a milder form of the disease, usually lasting from 1–3 weeks, whereas adults tend to experience a much more severe form of the disease [3]. Case fatality can reach 2% for adults over 50 years of age. Persons with pre-existing chronic liver diseases have an increased risk of death from fulminant hepatitis A. Infection with HAV confer life-long immunity **[3]**.

Globally, hepatitis A is more common in regions of the world with poor sanitation and no enough safe water **[4]** and around 1.4 million symptomatic cases occur each year **[2]** and about 102 million infections (symptomatic and asymptomatic) **[5]**. In the developing world about 90% of children have been infected by age 10 and thus are immune by adulthood **[4]**. It often occurs in outbreaks in moderately developed countries where children are not exposed when young and vaccination is not widespread [4]. Acute hepatitis A resulted in 102,000 deaths in 2010 **[6]**.

NAC (N-acetyl cysteine) is frequently used as a mucolytic and as an antidote in paracetamol intoxication **[7-8]**. NAC may maintain cell integrity by increasing the amount of glutathione within the cell or coming into direct reaction with spontaneous conjugation and/or reduction **[9]**. The need for a treatment to shorten duration of acute viral hepatitis (AVH) is obvious, but it has not been found yet. This problem might be solved with NAC, which protects the cellular architecture by increasing the amount of intracellular glutathione that reacts with toxic free oxygen radicals **[10]**. NAC was initially patented in 1960 and licensed for use in 1968 **[11]**. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system **[12]**. It is available as a generic medication and is not very expensive **[12]**.

The objective of this study was to assess the effect of oral N-acetyl cysteine compared with placebo on length of hospital stay in adult patients who were admitted to hospital with acute hepatitis A which might cause earlier resolution of hepatitis.

SUBJECTS AND METHODS

This study was conducted between February 2014 and July 2015, at the Infectious Disease Hospital (IDH). The patients included in this study were diagnosed as acute hepatitis A. Diagnosis of acute hepatitis A was clinically based on the presence of symptoms, e.g. anorexia, nausea, vomiting, abdominal discomfort, fever, fatigue and jaundice and confirmed serologically by positive of HAV Immunoglobulin M (IgM) antibodies, indicating acute disease.

40 patients were diagnosed as acute hepatitis A and divided into two groups, the first one involved 20 patients who received oral N-acetyl cysteine and supportive treatment, and the second one involved also 20 patients but they received placebo and supportive treatment. All patients were subjected to history taking and thorough clinical examination. We measured liver function test (LFT), kidney profile (KP), complete blood count (CBC), blood glucose, C-reactive protein (CRP) and coagulation profiles on the day of presentation, and every other day till the day of discharge from the hospital. Also, Serological tests were done for HBsAg, HBcIgM, antibody to Hepatitis C virus and antibody to hepatitis delta virus to exclude other causes of acute viral hepatitis.

Patients in the first group (NAC group) were given 600 mg NAC effervescent tablet orally once daily (600 mg/day), NAC was continued as long as required for normalization of laboratory investigations and the patients in the second group were given placebo orally 3 times a day (placebo group). All patients received supportive treatment, according to individual needs. The study protocol was approved by the local ethics committee. All patients were informed to participate in by an inscription form in the study.

Statistical Analysis :

The data were analyzed using the statistical package for social sciences (SPSS) version 8.0 software. The significance of differences between mean values of the study variables was evaluated by using t-test. The significance of differences between proportions was performed using the Chi-square test. Significant differences were expressed at $P<0.05$.

RESULTS

Forty patients were enrolled in this study, they were divided into two groups, N-acetyl cysteine group and placebo group, each of them involved 20 male patients varying in age from 14 years to 29 years. Of these, 11 patients were Indian, 10 Egyptian, 2 Indonesian, 8 Syrian, and 9 Kuwaiti. Symptoms at presentation included fever, anorexia, nausea, vomiting, abdominal discomfort, fatigue, dark urine and jaundice.

At the time of admission, there were no significant differences between the NAC group and the placebo group as regard to liver enzymes, Total bilirubin, direct bilirubin, INR, platelets, white blood cells, C-reactive protein, and serum creatinine (Table I).

After 5 days of admission, we noted a significant decline in liver enzymes (ALT & AST) and total bilirubin in the NAC group than the placebo group (table II). At time of discharge, there were no significant differences between the two groups as regard liver enzymes, total bilirubin, direct bilirubin, INR, platelets, white blood cells, C-reactive protein, and serum creatinine (Table III).

The mean length of hospital stay in the NAC group was 13.2 days (±0.67) compared with 14.3 days (±0.75) in the placebo group. Length of

hospital stay differed significantly between groups (p-value = 0.03, table III). All patients were started the treatment within one hour of admission to hospital. The mean time of reliving symptoms at presentation was 3.6 days in the NAC group and 4.4 days in the placebo group. The mean time of reliving symptoms at presentation was significantly lower in NAC group than in the placebo group (p-value = 0.05, Table II).

Table I : Comparison between studied groups at time of admission

	On admission		
	NAC group	**Placebo group**	**P-value**
Age	18.1±4.6	17.5±4.1	0.6
ALT(U/L)	2574.21±157.2	2496.7±149.3	0.4
AST(U/L)	1865.4±103.8	1879.1±113.7	0.83
Total bilirubin (µmol/L)	34.5 ± 4.36	36.1 ± 3.04	0.23
Direct bilirubin (µmol/L)	18.7 ± 3.4	19.3 ± 3.6	0.12
Albumin (g/L)	38.5 ± 5.4	38.8 ± 4.2	0.85
CRP	13.04±3.03	13.05±3.06	1.0
INR	1.43±0.3	1.33±0.4	0.78
Platelet	171.9±4.3	173.5±4.1	0.94
WBCs	6.7±1.3	6.34±1.4	0.83
S. creatinine (µmol/L)	89.32±14.12	88.76±13.23	0.89

NAC = N-acetyl cysteine; ALT= Alanine transaminase; AST= Aspartate aminotransferase; CRP= C-reactive protein; INR= international normalized ratio; WBC= White blood cells; S. creatinine= Serum creatinine.

Table II : Comparison between studied groups after 5 days from admission

	After 5 days from admission		
	NAC group	**Placebo group**	**P-value**
ALT	1057.1±78.2	1409.3±86.2	0.05
AST	503.2±60.1	851.4±49.3	0.04
Total bilirubin (µmol/L)	24.3 ± 3.4	28.2 ± 3.1	0.04
Direct bilirubin (µmol/L)	11.5 ± 2.5	13.3 ± 2.4	0.1
Albumin (g/L)	35.1 ± 4.4	35.9 ± 4.2	0.24
CRP	9.0±3.2	8.0±3.4`	0.62
INR	1.23±0.2	1.26±0.4	0.81
Platelet	184.5±26	183.7±23	0.86
The mean time of reliving symptoms (day)	3.6±0.37	4.4±0.7	0.05

NAC = N-acetyl cysteine; ALT= Alanine transaminase; AST= Aspartate aminotransferase; CRP= C-reactive protein; INR= international normalized ratio; WBC= White blood cells; S. creatinine= Serum creatinine.

Table III: Comparison between studied groups at time of discharge

	On discharge		
	NAC group	**Placebo group**	**P-value**
ALT	250.35±21.97	251.90±26.86	0.92
AST	134.5±12.4	139.9±16.8	0.8
Total bilirubin (µmol/L)	17.3 ± 2.1	18.1 ± 2.2	0.12
Direct bilirubin (µmol/L)	7.5 ± 1.3	8.3 ± 1.4	0.61
Albumin (g/L)	36.2 ± 4.1	35.7 ± 4.1	0.65
CRP	4.7±1.5	4.75±1.3	0.93
INR	0.96±0.2	1.08±0.24	0.29
Platelet	191.74±18.5	189.0±20.6	0.53
WBCs	8.44±1.76	8.41±1.81	0.93
S. creatinine	84.3±11.4	85.5±11.78	0.74
Length of stay (day)	13.2±0.67	14.3±0.75	0.03

NAC = N-acetyl cysteine; ALT= Alanine transaminase; AST= Aspartate aminotransferase; CRP= C-reactive protein; INR= international normalized ratio; WBC= White blood cells; S. creatinine= Serum creatinine.

DISCUSSION

N-acetyl cysteine (NAC) is a specially modified form of the dietary amino acid cysteine. When taken orally, NAC is thought to help the body make the important antioxidant enzyme glutathione. It has shown promise for a number of conditions, especially chronic bronchitis **[13,14]**.

NAC has been proposed as supportive therapy for HIV. Despite some intriguing results, overall the evidence is inconsistent at best **[15,16,17]**. In addition, treatment of HBV-producing cell lines with NAC resulted in an at least 50-fold reduction of viral DNA in the tissue culture supernatant within 48 hours **[18]**. Recently, some studies have shown good results and absence of side effects in patients treated with NAC in hepatitis B and chronic hepatitis C patients **[19,20]**.

The complications due to acute viral hepatitis were considered to be more frequent in adults than in the pediatrics **[20]**. Recently, reports from hepatic transplant centers suggest that 26% of cases with acute liver failure are caused with acute hepatitis A **[21]**. Hepatitis A is a common infection in the world and 50% of the population aged up to 15 and 90% of the adults are exposed to this disease **[22]**.

When acute hepatitis A (AHA) displays a symptomatic presentation, it is generally cured at the end but after a long course. In this study, we noted the mean time of reliving symptoms at presentation was significantly lower in the NAC group than in placebo group. In the first 5 days after admission, we noted that the NAC group showed a much more rapid improvement in liver enzymes and total bilirubin than the placebo group. Also, in this trial, we noted an overall reduction in mean length of hospital stay of more than one day in patients with AHA who were given NAC compared with who were given placebo. These findings support our hypothesis that adjunctive treatment of AHA with oral NAC might change the immune response and thereby reduce morbidity and length of patients stay in hospital.

The optimal duration of administration of NAC is not well known up tell now **[23]**. In this study, the duration of administration of NAC was between 11 days and 14 days, without observation any undesirable side effects, e.g. nausea, vomiting, itching, rash, hypotension, bronchospasm **[17]**. This is in line with Huseyin et al. **[9]** and Hu **[24]**, who have shown that this drug is not harmful to patients with AVH.

The role of N-acetylcysteine (NAC), a glutathione precursor, in the treatment of acetaminophen-induced acute liver failure (ALF) is well established **[25]**. NAC has also been used in small trials in non-acetaminophen-induced ALF (NAI-ALF) with variable results **[26]**. The clinical basis for the use of NAC is based on several mechanisms, of which the most important are: a) to facilitate the synthesis of depleted glutathione in AHA, and replenish hepatic stores of glutathione, b) it has vasodilating effects which improve microcirculatory blood flow and oxygen delivery to vital organs **[27]**, c)

increasing the blood flow by increasing the soluble nitric oxide activity in the gultamyl cyclase system, d) it acts as antioxidant that scavenges the free radicals **[27]**, e) blocking oxidative stress and avoiding the accentuation of hepatic damage **[28]**.

There are limited data addressing the use of oral NAC in the treatment of AHA. We could not find any study that focused on the effects of NAC on AHA except one published study investigating the effect of NAC on AVH (A & B), it was determined that NAC had no effect on the jaundice duration in AVH infection and the period in which the ALT value came back to normal and accordingly hospitalization duration of AVH patients and the prognosis of biochemical parameters **[9]**.

CONCLUSION

This study reported that the use of oral NAC as adjunctive therapy for treatment of acute hepatitis A was associated with a shorter length of hospital stay. We also found that the use of NAC was safe in these patients. There is an undoubted necessity for further research into the treatment of hepatitis A, and this study has identified a promising compound NAC, that may be an integral component of future HAV management.

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