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 affecting 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 the hospital with acute hepatitis A which might cause earlier resolution of hepatitis.

Subjects and Methods: 40 patients were diagnosed as acute hepatitis A and classified 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 complete blood count (CBC), kidney profile (KP), liver function test (LFT), 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), HEV 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 safe in these patients and was associated with a shorter length of patient stay in the hospital.

INTRODUCTION

Hepatitis A is an acute, self-limiting disease affecting the liver caused by 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, who are infected, recover completely with no permanent liver damage **[2]**. Acute hepatitis A does not become chronic and there is no chronic carrier state. On rare occasions the disease may be very severe, with fulminant hepatitis, hepatic coma and death [2]. Severity of illness is strongly age dependent; adult who are infected with acute hepatitis A tend to experience a much more severe form of the disease, whereas young children typically have a milder form of the disease, usually lasting from 1–3 weeks [3]. For adults over 50 years of age, case fatality can reach 2%. The increased risk of death from fulminant hepatitis A can occur in persons with pre-existing chronic liver diseases. Infection with HAV confers life-long immunity **[3]**.

Globally, hepatitis A is more common in regions of the world drinking contaminated water and with poor sanitation **[4]** and around 1.4 million symptomatic cases occur each year **[2, 5]**.The adulthood are immune in the developing world because about 90% of children have been infected by age 10 **[4]**. Outbreaks occur in developed countries where vaccination is not widespread and children are not exposed to the infections when young [4]. In 2010, acute hepatitis A caused 102,000 deaths **[6]**.

N-acetyl cysteine (NAC) can be used as an antidote in paracetamol intoxication and also can be used as a mucolytic **[7, 8]**. N-acetyl cysteine can increase the amount of glutathione within the cell and maintain cell integrity **[9]**. The necessity for a medicine to decrease the duration of acute viral hepatitis is obvious, but it has not been found yet. This problem might be solved with N-acetyl cysteine, which protects the liver cells architecture by increasing the amount of glutathione within liver cells that reacts with reactive oxygen species (ROS) **[10]**. NAC was licensed for use in 1968 **[11]**. It is on the World Health Organization's List of Essential Medicines, it is not very expensive drug, safe and most effective medicines needed in a health system **[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 the 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 confirmed diagnosis of acute hepatitis A and classified 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 complete blood count (CBC), kidney profile (KP), liver function test (LFT), 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, all patients were investigated for HEV IgM, hepatitis C virus antibody, HBsAg, HBcIgM, and hepatitis delta virus antibody 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.

Statistical Analysis:

The statistical package for social sciences (SPSS) version 8.0 software was used for analysis the data. The t-test was used to evaluate the significance of differences between mean values of the study variables. 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 included in the study, they were classified 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, no significant differences were noted 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, no significant differences were observed between the two groups regarding total bilirubin, direct bilirubin, liver enzymes, INR, platelets, white blood cells, C-reactive protein, and serum creatinine (Table III).

The mean length of patient stay in the hospital 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

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, particularly 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]**. Recently, some studies have revealed good results and absence of side effects in chronic hepatitis C and hepatitis B patients who treated with NAC **[18, 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 **[22]**.

When symptoms of acute hepatitis A (AHA) occur, recovery from these symptoms may take several weeks or months. 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 clarified that NAC is a safe drug to the patients with acute viral hepatitis.

The role of NAC, a glutathione precursor, in the treatment of paracetamol-induced acute liver failure (ALF) is well established **[25]**. Also, in small trials, NAC has been used in non-paracetamol-induced 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]**.

The data about using of oral NAC in the treatment of AHA are restricted. To our knowledge, there is no any study assessed the effects of NAC on AHA except one published study evaluating the effect of NAC on AVH (A & B), this article has shown that NAC did not have effect on the length of hospital stay of AVH infection and, on the period in which the ALT value came back to normal and also 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 might be beneficial in decreasing the length of hospital stay. It is also reported that the use of NAC was safe because of absence of its side effects 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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