A Study on the Role of N-Acetyl Cysteine Therapy in Acute Viral Hepatitis A

Vinod V. S.¹, Vijithkumar K.², Riyas C.³, Malini V. S.⁴, Arun S. Menon⁵

¹Associate Professor, Department of Internal Medicine, PK Das Institute of Medical Sciences, Palakkad, Kerala, India. ²Senior Consultant, Department of Internal Medicine, Valluvanad Hospital, Palakkad, Kerala, India. ³Assistant Professor, Department of Internal Medicine, PK Das Institute of Medical Sciences, Palakkad, Kerala, India. ⁴Assistant Surgeon, Community Health Centre, Ottapalam, Palakkad, Kerala, India. ⁵Senior Consultant, Department of Internal Medicine, Valluvanad Hospital, Palakkad, Kerala, India.

ABSTRACT

BACKGROUND
Hepatitis A is a viral infection of children and young adults but recently being noticed among adults also especially in developed countries. Infection is transmitted through ingestion of contaminated food or water or through direct contact with an infectious person. Viral replication occurs in liver only and the usual incubation period is 15-45 days. It is usually a self-limiting illness but at times can be fatal especially in elderly and patients with underlying chronic hepatitis C infection. Many medications have been tried till date without convincing evidences. N-Acetyl Cysteine (NAC) is a thiol and a precursor of L-cysteine and glutathione (GSH.) NAC helps the body to synthesize glutathione, the body’s master antioxidant which in turn protects the liver from damaging effect of toxins. Aim of this study was to look into the effects of NAC in acute viral hepatitis A.

METHODS
It was a prospective interventional study conducted in internal medicine department of a tertiary care teaching center of Palakkad district in Kerala. The study period was 5 months. All patients with symptoms suggestive of Hepatitis were considered. Those with IgM HAV positive serology were included in the study. Those with history of chronic liver disease or with positive serology for other viral liver infections were excluded from study group. They were divided into 2 groups by picking a lot and study group was given NAC. Patients in the control group were given standard symptomatic care. Paracetamol was not given to any of the patients even though many of them had already received paracetamol from elsewhere before admission. Biochemical parameters were followed up serially in both study and control groups till clinical and biochemical improvement is achieved. Data was analysed using Statistical Package for Social Sciences (SPSS) version 16.

RESULTS
No statistically significant association was found between the difference in total bilirubin, direct bilirubin, SGOT, SGPT and INR values on admission and discharge between the study and control groups.

CONCLUSIONS
Our study couldn’t demonstrate any significant role for NAC in viral hepatitis A. Further randomized studies taking into consideration a large sample size is required to prove the role of NAC in acute viral hepatitis A. however we didn’t observe any harmful effects with NAC administration to HAV patients.

KEYWORDS
Viral Hepatitis A, N-Acetyl Cysteine

J. Evid. Based Med. Healthc., pISSN- 2349-2562, eISSN- 2349-2570/ Vol. 7/Issue 22/June 01, 2020
Hepatitis A is a viral liver disease caused by Hepatitis A virus. It is an RNA virus and belongs to Hepatovirus genus of the picorna family. Infection is transmitted through ingestion of contaminated food or water or through direct contact with an infectious person. Viral replication occurs in liver only and the usual incubation period is 15–45 days. Usual age group affected is children and young adults. Hepatitis A is a self-limiting disease but rarely it can cause acute liver failure which can be fatal.\(^1\)\(^2\) According to WHO estimates about 1.4 million cases of Hepatitis A occurs every year worldwide.\(^3\)

Major cause of hepatic injury is host immune response to HAV. Viral replication happens in the hepatic cytoplasm and infected hepatocytes are destructed by CD8+ lymphocytes and natural killer cells. The prodromal symptoms include anorexia, nausea, vomiting, low grade fever, abnormal smell or taste. It is followed by dark coloured urine and soon clinical jaundice appears. Patient experiences right hypochondrial pain and tenderness due to liver enlargement. Patient may develop pruritus also. Physical signs include icterus, hepatomegaly less commonly splenomegaly and rarely extra hepatic manifestations in the form of rash and arthralgia. This is followed by recovery phase during which constitutional symptoms disappear but hepatomegaly and biochemical abnormalities will persist.

Majority (85%) of the patients show clinical and biochemical recovery within 3 months but it may be prolonged up to 6 months for a small number. Fulminant hepatic failure can occur as a rare complication of HAV infection especially in patients more than 50 years or those with underlying chronic hepatitis C infection. Diagnosis is by detection of antibodies to HAV. Initial antibody response is that of IgM type and later by convalescence IgG will be the predominant one. IgM usually persists for 3–6 months and disappear but IgG remains indefinitely offering lifelong protection from further HAV infection. There is no effective treatment for Hepatitis A, many medications have been tried but none have shown to be superior to placebo and hence not recommended for routine use.\(^4\)

N-Acetyl cysteine (NAC) is a thiol and a precursor of L-cysteine and glutathione (GSH). NAC helps the body to synthesize glutathione, the body's master antioxidant. Since it is a glutathione precursor, NAC protects the liver from the damaging effects of toxins – a function that can prevent chronic liver disease from advancing to a more severe illness.\(^5\) NAC is the source of sulphydryl groups and a scavenger of free radicals. NAC has been shown to interact with many metabolic pathways, such as regulators of the cell cycle, apoptosis, gene expression, and signal transduction, and also immune system. The most established clinical application of NAC is to prevent fulminant hepatic failure caused by paracetamol poisoning. The application of NAC in treatment of many diseases like cancer, human immunodeficiency virus (HIV) infection, cardiovascular diseases and liver diseases have been under study.\(^6\)\(^7\)

We wanted to investigate the effect of NAC in Acute viral Hepatitis A infection.
Data Analysis
All data were entered into Microsoft excel sheet and analysed using Statistical Package for Social Sciences (SPSS) software version 16. The categorical variables have been summarized using frequencies and proportions. The quantitative data were summarized with mean and standard deviation for normally distributed data. The difference in total bilirubin, direct bilirubin, SGOT, SGPT, INR values on admission and discharge between the study and control groups were tested for statistical significance using independent sample t test.

Ethical Consideration
The clearance from the Institutional Ethics Committee was obtained prior to the study. The nature of the study was explained and written consent from each of the study participants were obtained prior to the study. Privacy and confidentiality of all the information collected was maintained throughout the conduct of the study.

RESULTS
A total of 36 patients diagnosed as having Hepatitis A infection participated in the study. There were 23 participants in the study group and 13 participants in the control group. The mean age of the study participants was 24.28 years (SD ± 6.07). Minimum age was 9 years and maximum age was 40 years. A total of 24 males and 12 females participated in the study. Most of the patients presented with icterus and abdominal pain. NAC was administered to patients in the study group as an infusion.

| Variable                         | Study Group (n=23) | %   | Control Group (n=13) | %   |
|----------------------------------|--------------------|-----|----------------------|-----|
| Pruritus                         | 4                  | 17.4| 1                    | 7.7 |
| Mucocutaneous bleed              | 0                  | 0   | 0                    | 0   |
| Altered sensorium                | 0                  | 0   | 0                    | 0   |
| Abdominal pain                   | 7                  | 30.4 | 9                    | 69.2 |
| Icterus                          | 20                 | 97   | 13                   | 100  |
| Flap                             | 0                  | 0   | 0                    | 0   |
| Hepatomegaly                     | 15                 | 65.2 | 3                    | 61.5 |
| Splenomegaly                     | 1                  | 4.3  | 1                    | 7.7  |
| Ascites                          | 0                  | 0   | 1                    | 7.7  |

Table 1. Frequency of Clinical Symptoms in the Study and Control Groups

Paracetamol was not given to any of the patients during the course of stay in hospital, but many patients received paracetamol from other treatment facilities.

| No. of Days NAC Given | Frequency (n=23) |
|-----------------------|------------------|
| 1                     | 3                |
| 2                     | 4                |
| 3                     | 10               |
| 4                     | 1                |
| 5                     | 3                |
| 7                     | 1                |
| 14                    | 1                |

Table 2. Frequency of NAC Treatment in the Study Group

Mean cumulative dose of paracetamol was 2.09 gm (+2.9) in the study group and 2.08 gm (+2.1) in the control group (p=0.05). Complementary and alternative medicine practices (CAMS) like Ayurveda and herbal remedies were reported by a proportion of patients before admission.

| CAMS Treatment | Study Group (n=23) | %   | Control Group (n=13) | %   | P Value |
|----------------|--------------------|-----|----------------------|-----|---------|
| Yes            | 10                 | 43.5 | 7                    | 53.8 | 0.73    |
| No             | 13                 | 56.5 | 6                    | 46.2 |         |

Table 3. Paracetamol Ingestion before Admission

The difference in total bilirubin levels on admission and discharge was found out for each participant in the study and control groups. Independent sample t test was done to find out the association between difference in total bilirubin values on admission and discharge between the study and control groups. Similarly the difference in direct bilirubin, SGOT, SGPT and INR values on admission and discharge was also found out for each participant in the study and control groups and independent sample t test was done to find out the association between the above said parameters in both the groups.

| Variable              | t Value | P Value |
|-----------------------|---------|---------|
| Total Bilirubin       | 0.161   | 0.873   |
| Direct Bilirubin      | 0.210   | 0.835   |
| SGOT                  | 0.261   | 0.796   |
| SGPT                  | 0.302   | 0.765   |
| INR                   | 0.272   | 0.787   |

Table 5. Comparison of Study and Control Groups

No statistically significant association was found between the difference in total bilirubin, direct bilirubin, SGOT, SGPT and INR values on admission and discharge between the study and control groups. Thus from bivariate analysis, in this study it is found that the administration of N-acetyl cysteine to the study group had no significant role in modification of biochemical parameters when compared to the control group.

DISCUSSION
Acute viral Hepatitis A is a public health problem in many developing countries including India. It is one of the leading
causes of vaccine preventable infections acquired by the travellers. Hepatitis A infection is usually acquired through faeco-oral route but at times through sexual contact or rarely through illicit drug use. It is mainly a disease of children and young adults but usually it is a self-limiting illness and it displays a long course.

Major goal in the management of hepatitis A infection is to prevent infection. Humans are the only known reservoir for HAV and hence it can be successfully eradicated with appropriate preventive strategies. The major tools to this are attention to hygienic practices, vaccination and IV immunoglobulin. Prior to hepatitis A exposure vaccination is better than immunoglobulin. Post exposure prophylaxis is to give a single dose of HAV vaccine or immunoglobulin as early as possible but not beyond 2 weeks after exposure to infection.

Hospitalization is indicated for patients with severe symptoms only. Even though strict bed rest is not recommended most of the patients feel better with restricted physical activity and hence shall be advised. A high calorie diet especially in the morning is preferred. Universal precautions including proper hand washing should be emphasized. Physical isolation with single room and separate washroom is not necessary. Universal precautions including proper hand washing should be emphasized. Physical isolation with single room and separate washroom is not necessary.

Usual treatment protocol includes supportive care with avoidance of medications that can cause liver damage and cautious use of medications which are metabolized through liver. Various medicines like steroids, interferon, ursodeoxycholic acid have been tried in its treatment but none has been found superior to placebo and hence not recommended for routine use.6,9,10 So there is lack of a drug that can actually cure or modify the clinical course of acute viral hepatitis A. We thought NAC may be of help.

N-Acetyl cysteine is in clinical practice for many years but mainly it is used as a mucolytic agent or as an antidote for paracetamol intoxication. In Paracetamol intoxication it is used to replenish the glutathione stores. It exerts its mucolytic action through its free sulfhydryl group which opens up the disulfide bonds in glycoproteins. No dosage adjustment is necessary for patients with renal or hepatic impairment. Major adverse reactions with intravenous use are pruritus, rash, urticaria, nausea, vomiting and anaphylactoid reactions. Here we conducted a randomized controlled trial to find out the effects of NAC on the clinical outcome as well as liver function tests in AVH.

This study determined that NAC administration had no effect on the course of Acute viral Hepatitis A. No significant decrease in Bilirubin, SGOT, and SGPT values were observed between the study and control groups. This result is in accordance with a study conducted by Gunduz et al on role of N- acetyl cysteine therapy in acute viral hepatitis.4 A study conducted by Khalid Mumtaz et al showed that NAC use is associated with reduction in non-acetaminophen induced liver failure and is safe to use.7 Recently many studies have proved that NAC was able to inhibit hepatitis B virus replication and suggested a combination of NAC and interferon therapy in Hepatitis B treatment.11 A study conducted by Badawy et al in albino rats showed that NAC in small doses is safe and can be used while in large doses it can be hepatotoxic.12

In this study it was found that there is no significant difference in biochemical parameters between the study and control groups. Clinically we could find a better reduction in liver enzyme levels in the study group but on statistical analysis it proved non-significant. This may be because of the small sample size and further studies taking into consideration a large sample size is required. However we didn't observe any harmful effect to patients with acute viral hepatitis while on N-acetyl cysteine.

CONCLUSIONS

Not many studies have been conducted investigating the effect of NAC on acute viral hepatitis A. NAC administration didn't change the liver enzyme activities in patients with acute viral hepatitis. The study determined that the use of NAC is no more effective than symptomatic treatment modalities in acute viral hepatitis. One of the limitations of this the study is the small sample size and hence the data could not be extrapolated into a large group. Further randomized studies with a large sample size are required to prove the role of NAC in acute viral hepatitis A.

REFERENCES

[1] World Health Organisation. Global Hepatitis report 2017. Available from www.who.int. (Accessed on 29/9/18)
[2] World Health Organisation. Hepatitis A fact sheet. Available from www.who.int. (Accessed on 26/9/18)
[3] Park K. Park's textbook of preventive and social medicine. 23rd edn. Jabalpur: M/S Banarsidas Bhanot Publishers 2015.
[4] Gunduz H, Karabay O, Tamer A, et al. N-acetyl cysteine therapy in acute viral hepatitis. World J Gastroenterol 2003;9(12):2698-2700.
[5] Liver antioxidants. What to pair with NAC. www.liversupport.com/liver-antioxidants-what-to-pair-with-nac/ (Accessed on 3/10/18).
[6] Wang C, Xia Y, Zheng Y, et al. Protective effects of N-acetylcysteine in concanavalin A-induced hepatitis in mice. Mediators Inflamm 2015;2015:1-7.
[7] Mumtaz K, Azam Z, Hamid S, et al. Role of N-acetyl cysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation. Hepatol Int 2009;3(4):563-570.
[8] Maier I, Wu GY. Hepatitis C and HIV co-infection: a review. World J Gastroenterol 2002;8(4):577-579.
[9] Ryder SD, Beckingham D. ABC of diseases of liver, pancreas, and biliary system: acute hepatitis. BMJ 2001;322(7279):151-153.
[10] Gregory PB, Knauer CM, Kempson RL, et al. Steroid therapy in severe viral hepatitis. A double-blind,
randomized trial of methyl-prednisolone versus placebo. N Engl J Med 1976;294(13):681-687.

[11] Weiss L, Hildt E, Hofschneider PH. Anti-hepatitis B virus activity of N-acetyl-L-cysteine (NAC): new aspects of a well-established drug. Antiviral Res 1996;32(1):43-53.

[12] Badawy AH, Abdel Aal SF, Samour SA. Liver injury associated with N-acetylcysteine administration. Journal of the Egyptian Society of Parasitology 1989;19(2):563-571.