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Assessing the effect of N-acetylcysteine in the survival of subjects having acute liver failure

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***Abstract*---**Background: Acute liver failure (ALF) is a rare syndrome, characterized by acute derangement of liver function and carries a high mortality. Indeterminate ALF still forms a significant number of cases in India as well as in the world. A prospective case-control study was carried to determine the effect of N-Acetylcysteine (NAC) on the survival of indeterminate ALF patients. Methods: A total of 30 patients with a diagnosis of indeterminate ALF were included in the study. 14 patients received NAC infusion for 72hrs whereas 16 patients in the control group received placebo. The parameters evaluated were demographic, clinical, biochemical, outcome, and length of hospital stay.Results: The two groups were comparable for the various baseline characteristics (demographic, clinical, biochemical, etc.). A total of 18 of 30 (60%) patients died with ALF complications; 6 (42.8%) patients belonged to NAC group and 12 (75%) patients to Control group (P = 0.077). The overall survival was not improved by NAC in indeterminate ALF. The use of NAC also did not reduce the duration of hospital stay of surviving patients (P = 0.409). Conclusion: The overall survival was not improved by NAC in indeterminate ALF. NAC administration did not reduce the duration of hospital stay.

***Keywords*---**acute liver failure (ALF), indeterminate ALF, hepatic encephalopathy (HE), N-Acetylcysteine (NAC).

Introduction

Acute Liver Failure (ALF) is a clinically challenging entity associated with unknown etiology and very high mortality rates. It is characterized by coagulation disorders, jaundice, hepatocellular insufficiency, and hepatic encephalopathy with no history of liver disease. ALF is a rare entity with new cases reported every year. Nearly 7% of all deaths related to liver-related causes are contributed by acute liver failure.[1] Approximately 6% of all liver transplants are due to ALF. Spontaneous recovery is seen in nearly 45% of the subjects with ALF. However,

effective treatment for etiologies when identified can be done. It is characterized by an INR of >1.5 associated with mental encephalopathy lasting for more than 26 weeks.[2]

ALF has heterogenous etiology wide high ecologic variation. The vital step in ALF management is to assess etiology to aid in targeted antidots and therapies, if available. The common etiology associated with ALF was toxins, autoimmune factors, herbal medications, and viral agents. One of the most common causes of ALF in European countries is the overdose of Acetaminophen, whereas, in Africa and Asia, viral hepatitis was the most common etiology seen. Other reported etiologies are autoimmune hepatitis, Wilson's disease, ischemic liver injury, viral hepatitis, and/or drug-induced liver injury. In India and globally, the most common cause for ALF was found to be Viral hepatitis causing nearly 90% ALF.[3]

N-acetylcysteine is an agent containing thiol and is a scavenger for free radicals that replenish cytosolic glutathione and cellular mitochondria, and has proved to have vasodilating, inotropic, antioxidant, and anti-inflammatory effects. It helps in ALF by improving oxygen delivery to the tissues and systemic hemodynamics. It can also help ALF subjects by posing favorable effects on the liver which is injured acutely. However, its use has not been studied widely. Literature data of N-acetylcysteine effect on subjects having Acute Liver Failure with causes other than acetaminophen overdose is scarce in the literature.[4] Hence, the present prospective case-control study was carried to determine the effect of N-Acetylcysteine (NAC) on the survival of indeterminate ALF patients.

Materials and Methods

The present prospective case-control study was carried to determine the effect of N-Acetylcysteine (NAC) on the survival of indeterminate ALF patients. The study was conducted at Wockhardt Hospital And Vasantrao Pawar Medical College and Hospital, Nashik, Maharashtra from December 2019 to December 2021 after obtaining clearance from the concerned Ethical committee. After explaining the detailed study design, informed consent was taken from all the subjects in both written and verbal form. The study included a total of 28 subjects from both genders having indeterminate acute liver failure.

The inclusion criteria for the study were subjects of age 18 years or more having ALF, INR >1.5, illness for less than 26 weeks, encephalopathy, no history of liver disease, and who were willing to participate in the study. The exclusion criteria were subjects having hepatic shock, pregnant subjects with ALF, autoimmune ALF, drug-induced ALF, viral ALF, and the subjects who were not willing to participate in the study. After the final inclusion of the study subjects, detailed history was taken and physical examination was done for all the subjects. This was followed by recording the demographics followed by biochemical parameters including coagulogram and liver function test (LFT) which were considered as baseline values.

After a confirmed diagnosis of ALF was made, the diagnosis was done with biochemical and clinical features of hepatic failure, no hepatitis viral markers, no drug exposure, and no infection. Blood samples were collected under aseptic and

sterile conditions for a diagnosis of the etiology including iron profile, Wilson profile (serum ceruloplasmin, serum copper), ASMA (anti-smooth muscle antibody), ANA (anti-nuclear antibody), HCV (hepatitis C virus), hepatitis D virus (IgG and IgM anti-HDV), hepatitis E virus IgM (HEV-IgM), hepatitis A virus IgM (HAV-IgM), hepatitis B core IgM (HBc-IgM), and hepatitis B surface antigen (HBsAg).

In subjects where non-hepatotropic virus etiology was considered for the ALF, the serology for EBV (Epstein Barr virus), CMV (cytomegalovirus), and HSV (herpes simplex virus) were done. The radiologic assessment was done to rule out intrahepatic lesions, hepatic vascular abnormalities, and biliary processes. The 28 included subjects were then randomly divided into two groups of 14 subjects each where Group I subjects were treated with intravenous N-acetylcysteine intravenously for 72 hours and Group II subjects were treated with a placebo of 5% dextrose infusion for 72 hours.

Intravenous N-acetylcysteine was given in initial loading dose of 150 mg/kg over 1 hour, for next 4 hours the dose was changed to 12.5mg/kg/hr, and for the next 67 hours, the dose was changed to 6.25mg/kg/hr. Liver transplant options were given to the subjects. Standard supportive care was given to all the subjects to prevent developing complications. Hypoglycemia was prevented by infusion of intravenous dextrose. Lactulose enema and stress-related ulcers were prevented with proton pump inhibitors. In subjects where intracranial pressure was raised, mannitol infusion and midazolam sedation were given with fluid and electrolyte balance. Decerebrate posturing/hypertonia, abnormal pupillary reflexes, were considered as clinical signs to diagnose intracranial hypertension. In subjects where the spontaneous bleed was seen, vitamin K and fresh frozen plasma were given. In subjects where sepsis was suspected, urine and blood cultures were taken, and the subjects were treated based on sensitivity. Serum creatinine of >1.5mg/dl predicted renal impairment. Clinically treatment response was monitored with Encephalopathy grade and INR, PT, and bilirubin were used to biochemically assess the treatment response. Mortality and morbidity were also assessed in study subjects. All study subjects were followed till death or discharge from the hospital. The collected data were subjected to the statistical evaluation using SPSS software version 21 (Chicago, IL, USA) and one-way ANOVA and t-test for results formulation. The data were expressed in percentage and number, and mean and standard deviation. The level of significance was kept at $p<0.05$.

Results

The present prospective case-control study was carried to determine the effect of N-Acetylcysteine (NAC) on the survival of indeterminate ALF patients. The study included a total of 28 subjects from both genders having indeterminate acute liver failure. The demographic characteristics of the study subjects are listed in Table 1. The mean age of the study subjects differed insignificantly from Group I and Group II was 35.3±16.4 and 33.7±20.4 years respectively. Group, I and Group II had 57.14% (n=8) and 64.28% (n=9) females respectively which showed statistically non-significant differences (p=0.963). Coma grade and duration from jaundice to encephalopathy also showed statistically non-significant differences between two groups with respective p-values of 0.591 and 0.614 respectively. In

liver parameters, creatinine, albumin, ALT, AST, and bilirubin all at baseline were statistically non-significant between two groups with p-values of 0.628, 0.325, 0.483, 0.843, and 0.416 respectively. INR was also comparable between the two groups having values of 2.4±0.9 and 2.2±0.7 respectively (p=0.505) as shown in Table 1.

The present study also assessed the duration of hospital stay in subjects who survived following acute liver failure and the results are summarized in Table 2. The study results have shown that the mean duration of hospital stay in subjects who survived was 9.2±4.4 days in Group I subjects that received N-acetylcysteine for 72 hours for acute liver failure, whereas, for subjects from Group II who received a placebo of 5% dextrose had mean hospital stay duration of 11.4±4.3 days. This difference was statistically non-significant with p=0.407. The range of duration for hospital stay was 6-14 days for Group I and group II, the stay duration was 8-15 days as shown in Table 2.

On assessing the survival rates in the two groups of the study subjects, it was seen that the subjects of Group I that received N-acetylcysteine for 72 hours had a survival rate of 57.14% with survival seen in 8 subjects, whereas, in Group II where subjects received 5% dextrose as placebo treatment, 3 subjects (21.42%) survived compared to Group I. This difference was statistically non-significant with a p-value of 0.075 as shown in Table 3.

Discussion

The present prospective case-control study was carried to determine the effect of N-Acetylcysteine (NAC) on the survival of indeterminate ALF patients. The study included a total of 28 subjects from both genders having indeterminate acute liver failure. The mean age of the study subjects differed insignificantly from Group I and Group II was 35.3±16.4 and 33.7±20.4 years respectively. Group, I and Group II had 57.14% (n=8) and 64.28% (n=9) females respectively which showed statistically non-significant differences (p=0.963). Coma grade and duration from jaundice to encephalopathy also showed statistically non-significant differences between two groups with respective p-values of 0.591 and 0.614 respectively. In liver parameters, creatinine, albumin, ALT, AST, and bilirubin all at baseline were statistically non-significant between two groups with p-values of 0.628, 0.325, 0.483, 0.843, and 0.416 respectively. INR was also comparable between the two groups having values of 2.4±0.9 and 2.2±0.7 respectively (p=0.505). These results were consistent with the findings of Bemeur C et al[5] in 2010 and Darweesh SK et al[6] in 2017 where authors assessed subjects with comparable demographics to the present study.

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duration was 8-15 days. These results were in agreement with the studies of Squires JE et al[7] in 2018 and Nabi T et al[8] in 2019 where authors have shown similar hospital stay in subjects with ALF as in the present study.

The present study also assessed the survival rates in the two groups of the study subjects, the results have shown that the subjects of Group I that received N-acetylcysteine for 72 hours had a survival rate of 57.14% with survival seen in 8 subjects, whereas, in Group II where subjects received 5% dextrose as placebo treatment, 4 subjects (28.57%) survived compared to Group I. This difference was statistically non-significant with a p-value of 0.075. These results were comparable to the studies by Ostapowicz G et al[9] in 2002 and Nabi T et al[10] in 2017 where authors have shown comparable survival rates in subjects following treatment of Acute Liver Failure.

Conclusion

Within its limitations, the present study concludes that N-acetylcysteine does not significantly improve the survival rates in subjects with ALF (Acute Liver Failure) when compared to placebo treatment with 5% dextrose, and did not decrease the duration of hospital stay. However, the present study had a few limitations including a small sample size, short monitoring time, and geographical area biases. Hence, more longitudinal studies with a larger sample size and longer monitoring period will help reach a definitive conclusion.

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Tables

Characteristics	Group I % (n)	Group II % (n)	p-value
Gender			
Females	57.14 (8)	64.28 (9)	0.963
Males	42.85 (6)	35.71 (5)	
Age (years)	35.3±16.4	33.7±20.4	0.812
Coma Grade	2.6±0.11	2.4±1.3	0.591
Jaundice to encephalopathy duration (days)	32±15.6	35±16.4	0.614
Creatinine (mg/dl)	1.5±0.7	1.6±0.8	0.628
Albumin (g/dl)	2.9±0.8	2.7±0.3	0.325
ALT (mg/dl)	1112±676	947±597	0.483
AST (mg/dl)	1012±782	965±510	0.843
Bilirubin (mg/dl)	18.3±8.7	20.6±9.7	0.416
INR	2.4±0.9	2.2±0.7	0.505
Hepatic encephalopathy			
Grade I-II	42.85 (6)	35.71 (5)	0.303
Grade III=IV	50 (7)	71.42 (10)	
Vomiting	35.71 (5)	28.57 (4)	0.663
Fever	35.71 (5)	42.85 (6)	0.795

Table 1: Demographic characteristics of the study subjects

Duration	Group I	Group II	p-value
Hospital stay duration			0.407
Mean± S. D	9.2±4.4	11.4±4.3	
Range	6-14	8-15	

Table 2: Hospital stay duration in the survived study subjects

Parameter	Group I % (n)	Group II % (n)	p-value
Survival	57.14 (8)	28.57 (4)	0.075

Table 3: Survival rates in the two groups of study subjects