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ROLE OF N-ACETYLCYSTIENE IN ACUTE HEPATIC FAILURE

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ABSTRACT:

Introduction: Acute liver failure (ALF) may be fulminant. Fulminant hepatic failure is characterized by the development of hepatic encephalopathy within 8 weeks after the onset of acute liver disease. Coagulopathy is invariably present. A thiol-containing agent, N-acetylcysteine (NAC) scavenges free radicals of oxygen and nitrogen. Its use in Non acetaminophen induced (NAI) ALF is still not being used as regular practice due to variable results of studies. This study was designed to evaluate the outcomes of NAC in NAI-ALF patients in terms of their early recovery, ICU stay and safety index of the drug.
Methods: A cross- sectional prospective study was done in two private hospitals from March 2007 to February 2008. Group I included patients with NAC and conventional treatment and Group II consisted of conventional treatment only.
Results: Total of 55 patients with acute hepatic failure without drug intoxication were admitted during the study period. They were randomly divided into two groups. Out of 55 patients, 30 were in Group I and 25 were in Group II . In Group I out of 30 patients 3 died with a success of treatment in 90.0% cases and in group II out of 25 patients 4 died with the success rate of 84%.
Conclusion: Role of N-Acetylcysteine in Acute Hepatic Failure is encouraging. Therefore it is recommended that patients with acute hepatic failure may preferably be given NAC along with conventional treatment rather than treating them with conventional regimen alone.

Key Wards: Acute Liver Failure (ALF), Acute Hepatic Failure (AHF)
N-Acetylcysteine (NAC), Non acetaminophen induced (NAI)

INTRODUCTION:

Acute liver failure (ALF) is a rare but life-threatening condition in which metabolic and excretory functions of the liver are severely deranged. ALF distinctly differentiates from the last stages of chronic liver diseases, where acute liver insult is known as ''Acute on chronic'' liver failure. [1] Acute liver failure is further divided into (hyper-acute) Fulminant, sub-acute, and Classic acute liver failure. Fulminant hepatic failure is defined as the acute liver failure with the time between appearance of encephalopathy and jaundice with in 8 weeks after the onset of acute liver disease [2]. Coagulopathy is invariably present i.e. INR > 1.5.This is the diagnostic criteria of labeling a case as fulminant hepatic failure.

A thiol-containing agent, N-acetylcysteine (NAC) scavenges free radicals of oxygen and nitrogen. NAC replenishes cellular mitochondrial and cytosolic glutathione stores. Moreover, NAC has an anti-inflammatory effect by inhibiting the activation of macrophages and neutrophils. It also suppresses the release of inflammatory cytokines like TNF and IL-8.[3 10]

The role of NAC in the treatment of acetaminophen-induced (NAI) ALF is well established .[4] NAC being the free radicals scavenger prevents toxicity by limiting the formation and accumulation of N-acetyl-p-benzoquinone imine. It has also shown to improve the cerebral perfusion pressure. [5 19] Its anti-inflammatory, antioxidant and vasodilating effects which

improve the microcirculation and increase the oxygen delivery to the vital organs.[6 9 14]

NAC, being a versatile drug having multiple mechanisms of actions in acetaminophen poisoning, has been used. But in non-acetaminophen-induced ALF (NAI-ALF) [3 7 8] it is still not being used as regular practice due to variable results of studies. This study was designed to evaluate the outcomes [10 11] of NAC in NAI-ALF patients in terms of their early recovery, ICU stay and safety index of the drug.

PATIENTS AND METHODS:

A cross- sectional prospective study was conducted in two private hospitals during March 2007 to February 2008 (12 months). All the diagnosed patients of acute hepatic failure were included in this study i.e. appearance of encephalopathy and jaundice with in 8 weeks after the onset of acute liver disease [2]. Coagulopathy is found invariably present i.e. INR > 1.5. The record was maintained in a preset Proforma. Patients were randomly divided into two groups on the basis of NAC and conventional treatment; Group I (NAC plus conventional treatment) and Group II (Conventional treatment only). Patients of acute hepatic failure due to any drug intoxication were excluded from this study as well as patients with raised urea and creatinine were also excluded from the study. Informed written consent were taken.

Group 1 were administered oral NAC at a dose of 140 mg/kg, followed by 70 mg/kg, for a total of 17 doses, 4 hours apart within 24 hours of admission. All patients were managed with the conventional treatment. The treatment mainly involved continuous intravenous dextrose, broad-spectrum prophylactic antimicrobials and proton pump inhibitors. Fresh frozen plasma was given in those cases only in which patients had spontaneous bleed. Nasogastric tube was inserted for feeding purpose in patients with encephalopathy. Data was then entered and analyzed in SPSS version 15.0. Comparative, and Descriptive statistics were calculated.

RESULT:

Total of 55 patients with acute hepatic failure without drug intoxication were admitted during the study period. Out of 55 patients, 30 were in Group I and 25 were in Group II. In Group I, out of 30 patients 19 (63.3%) were males and 11 (36.7%) were females with male preponderant. Mean age was 32.0±16.8 years with an age range of 17-90 years. In Group II, out of 25 patients 16 (64.0%) were males and 9 (36.0%) were females with male preponderant. Mean age was 31.3±15.0 years with an age range of 18-85 years.

In Table I the Group I, mean hospital stay of the patients was 8.8±1.9 days with an ICU stay of 2-3days. Majority of patients came with mean GCS of 5.9±2.6. Plantar reflexes were found up-going in 19 (63.3%) patients, mute in 7 (27.3%) cases, and equivocal and down-going in 2 (6.7%) cases respectively. On physical examination 29 (96.7%) patients were jaundiced, 27 (90.0%) dehydrated, 26 (86.7%) anemic, and 12 (40.0%) with flapping tremors. In Group II, mean hospital stay of the patients was 10.0±1.9 days with an ICU stay of 4-5 days. Majority of patients came with mean GCS of 6.0±3.3. Plantar reflexes were found up-going in 15 (60.0%) patients, mute in 4 (16.0%) cases, and equivocal and down-going in 3 (12.0%) cases respectively. On physical examination 25 (100%) patients were jaundiced, 24 (96.0%) dehydrated, 23 (92.0%) anemic, and 10 (40.0%) with flapping tremors.

On blood screening the etiology in Group I, were 15 (50.0%) cases had hepatitis A, 8 (26.7%) cases had hepatitis E with none of them was pregnant, 4 (13.3%) cases cause could not be ascertained and 3 (10.0%) cases were hepatitis B (Table III). Out of 30 patients 3 died with a success of treatment in 90.0% cases (Table II, chart I). In Group II, the etiology were 14 (56.0%) cases had hepatitis A, 5 (20.0%) cases had hepatitis E with none of them was pregnant, 1 (04.0%) case cause could not be ascertained and 5 (20.0%) cases were hepatitis B(Table III). Out of 25 patients 4 died with a success of treatment in 84.0% cases (Table I, Chart I). Blood hematology and chemistry on 1st day and 5th day of both groups were compared in Table I. In Table II the parameters are characterized according to the variable used in the King's College Hospital (KCH) criteria.

Out of 30 patients in Group I only 2 patients were noticed with the side effects of NAC, one patient had mild body rashes which was self limited and 1 had severe vomiting which was treated

CHART I:

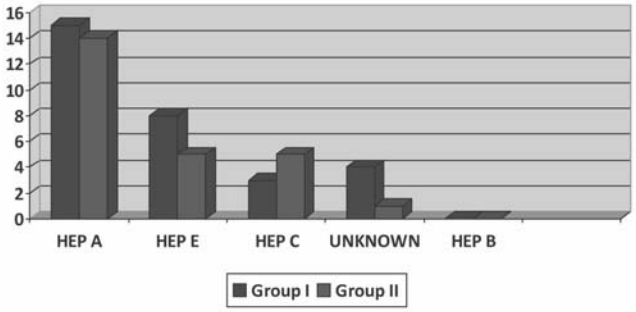


TABLE I:
BASIC CHARACTERISTICS

Labs values	Group I Mean values	Group II Mean values
Total Lecocyte Count day1	11060.0	12000.0
Total Lecocyte Count day5	9290.0	10000.0
Total Bilirubin day1	20.1	21.3
Total Bilirubin day5	10.9	12.6‘
Direct Bilirubin day1	12.6	12.8
Direct bilirubin day5	8.8	10.3
SGPTday1	3612.1	3514.8
SGPTday5	1432.8	1832.4
Alkaline Phosphatase day1	299.8	255.5
Alkaline Phosphatase day5	288.2	239.3
Serum Ammonia day1	344.5	350.1
Serum Ammonia day5	116.5	156.5
INRday1	2.8	3.0
INRday5	1.2	1.9
Serum albumin	3.9	3.5
Total protein	6.8	6.2
Urea	42.1	45.6
ICU stay	2-3 days	4-5 days
Mean Hospital Stay	8.8 +1.9 days	10.0+1.9 days
Success of treatment	90.0%	84.0%

Note Albumin, Urea and Creatinine were not significantly changed on day 5 from day one.

TABLE II:

King's College Hospital prognostic criteria-related factors in the two groups in this study

Parameters	Group 1	Group II	P Value
Prothrombin time			
<50	14	14	0.392
>50	16	11	
Bilirubin (mg/dl)			
< 17.6	17 (48.9 %)	14 (75 %)	0.019
>17.6	13 (51.1%)	11 (25%)	
Age			
< 40	12 (89.36%)	12 (63.63 %)	0.004
> 40	18 (10.64 %)	13 (36.37%)	
Interval between Jaundice and hepatic encephalopathy (days)			
< 7	19 (63.8 %)	14 (54.5%)	0.392
>7	11 (36.2%)	11 (45.5%)	
Success of treatment	90.0 %	84.0 %	

symptomatically.

DISCUSSION:

Acute viral hepatitis came as the foremost cause of acute liver failure accounting for up to 72 percent of all cases [12]. In this study 90.9% (50) cases had viral hepatitis and out of 50, 52.7% (29) patients had hepatitis A and 9.0% (5) cases had no etiology detected.

Hepatitis E virus is thought to have higher incidence of fulminant hepatic failure, the case fatality rate approaching 40 percent in pregnant women. but surprisingly in this study 23.6% (13) patients had hepatitis E virus but none of them was pregnant. Kortsalioudaki et al [12 13 14 15] reported shorter hospital stay in children with NAI-ALF using NAC [3]. In this study patients average ICU stay was decreased almost 50% from average 4-5days to 2-3 days; with a mean hospital stay of the patients was 8.8±1.9 days in Group I, in Group II not a significant decrease of ICU stay (4-5days average) was noticed with a mean hospital stay of 10.0±1.9 days, even higher then Group I [15].

Acute hepatic failure is a devastating disease which decreases the oxygenation of vital organs via vasoconstriction, N-Acetylcysteine owing to work on micro-vascular level by increasing cyclic 3', 5' Guanosine monophosphate (cGMP) levels and subsequently increases the nitric oxide levels causing vasodilation .[16 17 18 19 20] In this study fairly rapid recovery in patients were observed using NAC and only 3 patients died out 30 patients with a success of treatment in 90.0% cases in Group I. In Group II 4 patients died out of 25 and the success of treatment was 84.0%. All the dying patients were suffering from end stage chronic hepatitis B liver disease with a mean age 76.3 + 2.2 years. It is also noticed that NAC is a safe drug, only two patients were found to have mild body rash which was self limiting and one patient had severe vomiting episodes which was treated symptomatically.

CONCLUSION:

Role of N-Acetylcysteine in Acute Hepatic Failure is encouraging.

TABLE III : ETIOLOGY

Parameters	Group I	Group II	p Value
Characteristics	n = 30	n = 25	
Acute HAV	15	14	0..429
Acute HBV	3	5	0.392
Acute HEV	8	5	0.498
Unknown Cause	4	1	0.198

Therefore, it is recommended that patients with acute hepatic failure may preferably be given NAC along with conventional treatment rather than treating them with conventional regimen alone.

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