

## Role of N- Acetylcysteine in Fulminant Hepetic Failure

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### ABSTRACT

**Objective:** The objective of this study was to evaluate the efficacy of N-acetylcysteine in fulminant hepatic failure.

**Setting:** Department of Paediatrics, Lahore General Hospital, Lahore.

**Design:** Quasi experimental study.

**Period:** September 2008 to August 2010.

**Methods:** Sixty patients with fulminant hepatic failure were divided in 2 groups. Group A was given N-acetylcysteine 140mg/kg loading dose followed by 70mg/kg four hourly for 17 doses. Group B received only IV fluids, appropriate nutrition and drugs if needed. Patients were followed on daily basis for changes in clinical parameters like stages of encephalopathy and papillaedema on fundoscopy. The outcome measures were duration of encephalopathy, duration of hospital stay and final outcome like survival or death.

**Results:** The mean age of the patients in group A was 8.1±2.2 years and in group B was 8.3±2.2 years. The mean hospital stay in group A was 7.3±3.4 days and in group B was 9.1±3.4 days. The mean duration of encephalopathy of patients in group A was 5.4±2.5 days and in group B was 6.4±2.2 days. In the distribution of patients by final outcome, in group A, there were 24 (80%) patients who survived and 6 (20%) patients died. In group B, there were 19 (63.3%) patients who survived and 11 (36.7%) patients died.

**Key words:** Fulminant hepatic failure, N-acetylcysteine, hepatic encephalopathy.

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### INTRODUCTION

Fulminant hepatic failure (FHF) is the most feared complication of hepatitis in children. It is defined as clinical syndrome resulting from necrosis of hepatocytes or from severe functional impairment of hepatocytes in a patient who does not have a preexisting liver disease. The disorder usually evolves over a period of fewer than 8 weeks. Synthetic, excretory and detoxifying functions of the liver all are severely impaired with hepatic encephalopathy as an essential diagnostic criterion.<sup>1</sup> The incidence of FHF is 2,300 to 2,800 cases per year in the United States<sup>2</sup>. In Pakistan, viral hepatitis is endemic and almost all hepatitis A to G are prevalent here. Aziz et al in their study has mentioned prevalence of hepatotropic virus in population of age 14 years and below in Pakistan. According to this study Anti HAV is seen positive in 100%, Anti HEV 26.1, Anti HCV in 1.4% and Hbs Ag in 1.9% of the cases<sup>3</sup>.

Metabolic derangements in FHF include acute renal failure, electrolyte abnormalities, hypoglycemia, and pancreatitis. Renal failure complicates FHF in 40 to 50% of cases (70% of cases caused by acetaminophen) and denotes a poor prognosis<sup>4,5</sup>. It is

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often multifactorial, with causes including prerenal azotemia, acute tubular necrosis, toxic renal effect from an ingested agent, a functional disturbance (hepatorenal syndrome) or drug induced toxicity, e.g., antibiotics and contrast agents<sup>6</sup>. Because of impaired hepatic urea production, blood urea nitrogen levels do not reflect the severity of renal dysfunction and serum creatinine levels are thus preferred as a more accurate guide for monitoring renal function. Initial management should ensure adequate intravascular volume status, treat complicating infection, and avoid nephrotoxic agents. Hypoglycemia is a frequently encountered complication seen in up to 45% of FHF patients, as massive liver necrosis results in defective glycogenolysis, gluconeogenesis, and insulin metabolism<sup>7</sup>.

FHF results are fatal for most affected children. The mortality rate may reach 80-90% in the absence of liver transplantation. In some pediatric series, survival rates of 50-75% have been reported. Mortality can be reduced by regular monitoring of patients, fluid balance, drugs like antibiotics, lactulose, H<sub>2</sub> receptor antagonists, vitamin K and good nutritional support<sup>8</sup> N-acetylcysteine (NAC) has an established role as a antidote in acetaminophen toxicity<sup>8</sup> N-acetylcysteine also increases the cerebral blood flow which further increases the oxygen delivery to brain.<sup>9-10</sup> N-acetylcysteine is given in a dose of 140mg/kg orally followed by 70mg/kg after 4

hours for next 17 doses. Few adverse effects reported so far are nausea, vomiting<sup>11</sup>.

NAC has also been used for non-acetaminophen induced FHF. The NAC Study, a U.S. multicenter study of the safety and efficacy of NAC in the treatment of acute liver failure not caused by acetaminophen, is an important randomized study that will hopefully provide the necessary outcome (survival) data to answer this important clinical question. Study conducted in Israel has demonstrated improved survival<sup>10</sup>

The only therapeutic intervention of proven benefit for patients with FHF is that of emergency OLT. As there is no definite treatment of Fulminant hepatic failure except for supportive therapy so use of N-acetylcysteine decrease the mortality by reducing encephalopathy by improving cerebral blood flow and O<sub>2</sub> delivery. So objective of the study is to evaluate the therapeutic role of N-acetylcysteine in non-acetaminophen induced FHF in order to decrease mortality from such a grave disease in over set-up.

**METHODS**

This study was conducted in the Department of Paediatrics, Lahore General Hospital, Lahore. Quasi-experimental study. Children with fulminant hepatic failure of age between 1-14 years and of both sexes were included and children with chronic liver disease but now presenting with acute episode like Wilson disease and galactocimia and also acetaminophen induced fulminant hepatic failure were excluded from the study. Cases were divided into 2 groups, each group contained 30 patients.

Patients were diagnosed clinically. Patients were admitted through outpatient department and emergency department of Paediatrics, Lahore General Hospital Lahore. Exclusion criteria was strictly followed to control confounding variables. The purpose of study, risk and benefits were explained to parents of children and informed consent was taken. Group A was given N-acetylcyseine 140mg/kg loading dose followed by 70mg/kg four hourly for 17 doses diluted to a 5% solution in sweet fruit juices or carbonated soft drinks. It was given either orally in conscious patients or through nasogastric tube in comatosed patients. Appropriate nutrition, IV fluids and drugs like vitamin K, H2 receptor antagonists, antibiotics and lactulose were also given if needed. Group B received only IV fluids, appropriate nutrition and drugs if needed. Patient was followed on daily basis for changes in clinical parameters like stages of encephalopathy and papillaedema on fundoscopy. The outcome measures were duration of encephalopathy, duration of hospital stay and final

outcome like survival or death. Data was collected through specially designed proforma attached.

The collected data were entered into SPSS version 12 and analyzed accordingly. The study variables were age, sex, history, stages of encephalopathy, height, weight, hospital stay, duration of encephalopathy and final outcome. Simple descriptive statistics was calculated. The quantitative variables like age, height, weight, hospital stay and duration of encephalopathy were presented as mean and standard deviation. The qualitative variables like sex, history and stages of encephalopathy were presented in frequency and percentages. Student't' test was applied on numerical variables like hospital stay and duration of encephalopathy to find out the significance between the two groups. Chi square test was applied on final outcome (survived / death) to find out the significance between two groups. P value ≤0.05 was considered as significant.

**RESULTS**

Sixty cases meeting the inclusion criteria were included in this study. The mean age of the patients in group A was 8.1±2.2 years and in group B was 8.3±2.2 years. In group A there were 8 (26.7%) patients in the age group of 4-6 years, 15 (50%) patients in the age group of 7-9 years and 4 (13.3%) patients in the age group of 10-12 years. In group B, there were 6 (20%) patients in the age group of 4-6 years, 17 (56.7%) patients in the age group of 7-9 years, 7 (23.3%) patients in the age group of 10-12 years and 1 (3.3%) patients in the age group of 13-14 years (Table. 1)

In the distribution of patients by sex, in group A, there were 19 (63.3%) male patients and 11 (36.7%) female patients. In group B, there were 15 (50%) male patients and 15 (50%) female patients

Table 1: Distribution of patients by age

Age (Years)	Group A (n=30)		Group B (n=30)	
	No.	%age	No.	%age
4-6	8	26.7	6	20.0
7-9	15	50.0	17	56.7
10-12	4	13.3	7	23.3
13-14	0	0	1	3.3
Mean±SD	8.1±2.2		8.3±2.2	

All patients of group A presented with jaundice and encephalopahty while 7 (23.3%) patients also have bleeding manifestation. In group B, all patients presented with jaundice and encephalopathy, while 10 (33.3%) patients also have bleeding manifestation (Table. 2)

Table 2: Distribution of patients by sex

Sex	Group A (n=30)		Group B (n=30)	
	No.	%age	No.	%age
Male	19	63.3	15	50.0
Female	11	36.7	15	50.0
Total	30	100.0	30	100.0

The mean hospital stay in group A was 7.3±3.4 days and in group B was 9.1±3.4 days. In group A, there were 11(36.7%) patients in the hospital stay range of 1-5 days, 12(40%) patients of 6-10 days and 7 (23.3%) patients in the range of 11-15 days. In group B, there were 6(20%) patients in the hospital stay range of 1-5 days, 12(40%) patients of 6-10 days and 12 (40%) patients in the range of 11-15 days

The mean duration of encephalopathy of patients in group A was 5.4±2.5 days and in group B was 6.4±2.2 days. In group A, 8 (26.7%) patients in the duration of encephalopathy of 1-3 days, 13 (43.3%) patients of 4-6 days, 7 (23.3%) patients of 7-9 days and 2 (6.7%) patients of 10-12 days. In group B, there were there were 3 (10%) patients in the duration of encephalopathy of 1-3 days, 13 (43.3%) patients of 4-6 days, 11 (36.7%) patients of 7-9 days, 3 (10%) patients of 10-12 days (Table. 3)

Table 3: Distribution of patients by presenting symptoms

Presenting symptoms	Group A (n=30)		Group B (n=30)	
	No.	%age	No.	%age
Jaundice	30	100.0	30	100.0
Encephalopathy	30	100.0	30	100.0
Bleeding manifestations	7	23.3	10	33.3

In the distribution of patients by final outcome, in group A, 24 (80%) patients were survived and 6 (20%) patients were died. In group B, 19 (63.3%) patients survived and 11 (36.7%) patients were died (P<0.001) (Table 4).

Table 4: Distribution of patients by final outcome

Final outcome	Group A (n=30)		Group B (n=30)	
	No.	%age	No.	%age
Survived	24	80.0	19	63.3
Death	6	20.0	11	36.7
Total	30	100.0	30	100.0

df 1, P 0.001

## DISCUSSION

Fulminant hepatic failure is defined as clinical syndrome resulting from necrosis of hepatocytes or from severe functional impairment of hepatocytes in a patient who does not have a preexisting liver disease. The disorder usually evolves over a period of fewer than 8 weeks. Synthetic, excretory and detoxifying functions of the liver all are severely impaired with

hepatic encephalopathy as an essential diagnostic criterion.<sup>1</sup> Few studies have been conducted to evaluate the role of N-acetylcysteine in non acetaminophen induced Fulminant hepatic failure.

In our study, the mean age of the patients in group A was 8.1±2.2 years and in group B was 8.3±2.2 years. As compared to our study Kortsalioudaki et al has mentioned the mean age of 6.5 years<sup>12</sup>. Esklar has reported 58% male, 42% females and mean age 6.7± 3.5 years in his study<sup>13</sup>. In our study, in group A, there were 63.3% male and 36.7% female patients. In group B, there were 50% male and 50% female patients.

The mean hospital stay in group A was 7.3±3.4 days and in group B was 9.1±3.4 days. However Kortsalioudaki et al<sup>12</sup> has reported this period to be 8 days and 10 days respectively.

In our study, the mean duration of encephalopathy in group A was 5.4±2.5 days and in group B was 6.4±2.2 days. As compared with the study of Lee et al<sup>14</sup> the mean duration of encephalopathy in N-acetylcysteine group was 4 days and in patients given placebo group was 5 days, which is comparable with our study.

In our study, in group A, 80% patients were survived and in group B, 63.3% patients survived. Ben Ariz has reported survival rate of 57% and Keays et al 48% survival rate in N-acetylcysteine group<sup>15,16</sup>. Mumtaz Khalid et al has mentioned increase survival rate in N-acetylcysteine group<sup>17</sup>. In comparison to this Grant has mentioned no role of N-acetylcysteine in his study.

## CONCLUSION

It is concluded from this study that survival rate in patient of FHF given N-acetylcysteine has better survival rate than in patients without this therapy. So N-acetylcysteine group has more success rate and less mortality rate as compared to non-N-acetylcysteine group.

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