ORIGINAL ARTICLE

Non-Acetaminophen Induced Acute Liver Failure of Viral etiology: Treatment with and without N-Acetylcysteine; comparing the length of hospital stay and survival status in children at the tertiary care hospital

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Abstract

Background
Acetaminophen poisoning is a common cause of acute liver failure (ALF) and is treated with N-Acetylcysteine (NAC), which acts as an antidote, antioxidant and anti-inflammatory agent. NAC role in non-acetaminophen induced acute liver failure among children remains controversial and a few centers have adopted this option. Viral hepatitis (A and E) remains the leading cause of ALF in Pakistan. We aim to determine the role of NAC in ALF secondary to viral etiology.

Methodology
We performed this quasi experimental study at National Institute of Child Health, Karachi from December 2013 to December 2014**.** All Children of either gender between ages 5 to 13 years presented with viral induced ALF were enrolled. Children treated with NAC were included in group A and children not given NAC were enrolled in group B. NAC was administered as a continuous intravenous infusion (100 mg/kg/24 hours) until normalization of the INR or death. Standard care treatment was similar throughout the study period. The two groups were compared for the length of hospital stay, discharged or death.

Results
There were total 32 patients with 22 males and 10 females. Causes of ALF were HAV 23 (72%), Non A to E 5 (16%), HBV 3(9%) and both A and E in a patients. In group A, all 16 patients received NAC for median duration of 15.5 days. Length of hospital stay in group A was 14.4±6.7 days (median 15.5, IQR(11): 7.5 days to 18.5 days) while in group B it was 23.8±4.1 days (median 24, IQR(8): 19.5days to 27.5 days) p-value 0.001. Survival was higher in those who received NAC 11 (69%) than those who did not receive 7 (44%) but there was no statistically significant relationship was observed (p-value 0.154).

Overall mortality was found 44% (14 expired out of 32 patients).

Conclusion
There was no significant difference in overall survival of patients treated with NAC and without NAC. There was a significant improvement in survival observed in patients with early stage of encephalopathy grade 1& 2 treated with N-Acetylcysteine.

Keywords
Length of hospital stay, Survival status, N-Acetylcysteine, Acute liver failure

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Introduction

Acute liver failure (ALF) is a relatively uncommon but life threatening syndrome.[1] It is considered a medical emergency because of its multisystem involvement and association with high mortality rate.[2] The currently accepted definition in children includes biochemical evidence of acute liver injury (usually <8 wk duration), no evidence of chronic liver disease, and hepatic based coagulopathy defined as prothrombin time (PT) >15sec or international normalized ratio (INR) >1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or PT >20 sec or INR >2 regardless of clinical presence of hepatic encephalopathy.[3]

Intentional or unintentional acetaminophen poisoning has recently been evolved as most common etiology of acute liver failure in developed countries while in under developed countries; the most common etiology of ALF has been reported as viral and hepatitis A has been found as most frequent cause.[4,5,6] Published data regarding ALF in pediatric population from Pakistan reported viral etiology constitute approximately 75% of cases and reported mortality was in more than 50% of cases.[7,8] There is no specific treatment for ALF and supportive treatment is targeted to make patient hemodynamically stable, correcting coagulopathy, prevention or treatment of cerebral edema, coma care in unconscious patient and management of fluid, electrolytes and acid-base imbalances. Spontaneous recovery has been reported in 40% to 56% of pediatric patients with supportive treatment in different studies.[7,9]

Acetaminophen poisoning causing ALF is frequently treated with N-Actylcysteine (NAC), which acts as an antidote, an antioxidant and an anti-inflammatory agent. There was a study that suggested that NAC could also help children with non-

acetaminophen induced acute liver failure (NAI-ALF) by improving survival status and shortening hospital stay[10] which has led some medical centers to adopt this treatment modality.

The outcome of patients with ALF has been dramatically improved with liver transplantation.[11,12] In developing and underdeveloped countries this option is available only at few centers so we have to search for other modalities of treatment because in our part of world even at tertiary care set up liver transplantation facility is not available.[13]

Sotelo N *et al* described beneficial effect of NAC in NAI-ALF of viral etiology.[14] A recent retrospective single-center analytical study in children from Pakistan concluded that NAC showed improvement in LFTs and encephalopathy.[15] There is lack of prospective studies in treatment of ALF with and without NAC from developing countries. The objective of this study is to compare the length of hospital stay and survival status in children with and without NAC.

Methodology

A Quasi experimental study conducted at National Institute of Child Health, Karachi over a period of 1 year from December 2013 to December 2014. Sampling technique was non-probability consecutive sampling. Children of either sex, between the ages of 5 to 13 years, presenting with non-acetaminophen induced ALF of viral etiology, admitted to pediatric unit of NICH were included in the study. Children presenting with acetaminophen induced ALF or other etiologies like autoimmune hepatitis and Wilson disease were excluded from the study.

The acute liver failure was defined as presence of biochemical evidence of acute liver injury (usually <8 week duration), no evidence of chronic liver disease, prothrombin time (PT) >15sec or international normalized ratio (INR) >1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or PT >20 sec or INR >2 regardless of clinical presence of hepatic encephalopathy. The outcome was measured at the hospital discharge in terms of survival and duration of hospitalization. Survival was defined as discharge of patients from hospital from same admission and duration of hospitalization was defined as total duration of hospital stay from the day of taking N-Acetylcysteine.

An approval from local ethical committee was granted and a written informed consent was taken from the parents / guardians of the child. Clinical history was taken by the principal investigator. Age, sex, duration of stay in hospital, durations

of symptoms and duration between onset of initial symptoms and onset of encephalopathy, clinical signs and stage of encephalopathy were recorded.

Investigations including liver function test and prothrombin time (PT) were carried out. For etiology, viral markers for hepatitis A, B, C & E (anti HAV IgM, HBsAg, anti HCV antibody, anti HEV IgM) were done. The diagnosis of non-A to E hepatitis was made in cases with clinical presentation suggestive of viral etiology in the absence of any viral marker positivity and autoimmune hepatitis and Wilson diseases work up was negative. Subjects were randomly divided into study groups A and B by using lottery method. Group A included children routinely treated with NAC and Group B was of children not treated with NAC. NAC was administered as a continuous intravenous infusion (100 mg/kg/24 hours) until normalization of the INR or death. Standard care treatment was similar throughout the study period. This included continuous intravenous dextrose infusion to prevent hypoglycemia; broad spectrum prophylactic antimicrobials to prevent bacterial and fungal infections and antacids to prevent acute gastrointestinal bleeding. Children were admitted to the pediatric intensive care unit if they developed encephalopathy grade 2, became hypoxic, or needed sedation. Fresh frozen plasma was given only if an invasive procedure needed to be done. Infection was diagnosed only when a pathogenic microorganism was detected in blood, urine or tracheal cultures. The two groups were compared for the length of hospital stay, discharged or death. All the demographic and clinical data with laboratory finding and short term outcome after administration of NAC was collected on a predesigned proforma by the principle investigator.

Data was compiled and analyzed into SPSS 17. Mean ± SD was calculated for quantitative variable that is age and length of hospital stay, frequency and percentage was calculated for gender and survival. Median, IQR, Two sample‘t’ test was applied to compare length of the hospital stay in both groups, $p<0.05$ was taken as significant. Chi square test was applied to compare survival in both groups, taken $p<0.05$ as significant.

Results

Of total 32 patients,[16] patients were in each group i.e group A comprised of patients that were treated with NAC and group B patients did not receive NAC. There were 22 males and 10 females with 10 males and 6 females in group A and 12 males and 4 females in group B. Table 1 describes the clinical characteristics of all patients.

Mean age of the patients was 7.5±1.36 years in group A and 7.6±1.23 in group B. The minimum age of the patients was 5.5 while maximum age was 9.5 years.

Etiologies of ALF were HAV 23(71.9%), Non A to E 05 (15.6%), HBV 03(9.4%) and Combined A & E 01(3.1%) patients. As shown in table 1.

In group A, all 16 patients received NAC for median duration of 15.5 days.

The clinical features recorded in patients presenting with ALF were fever 21 (65.6%), loss of appetite 25 (78.1%), Nausea & vomiting 25 (78.1%), Abdominal pain 14 (43.8%), Jaundice 29 (90.6%), Hepatomegaly 23 (71.9%), Bleeding 10 (31.3%).

Regarding encephalopathy in group A patients presenting with grade I were 5(15.6%), grade II 7(22%), grade III 3(9.4%) and Grade IV 1(3.1%) while in group B grade I 6(18.7%), grade II 4(12.5%) , grade III 4(12.5%) and grade IV 2(6.2%). Seven patients in group A and 5 patients in group B developed encephalopathy within 7 days of illness (hyperacute) while 9 in group A and 11 in group B developed encephalopathy after 7 days of onset (acute). In terms of grade of encephalopathy and time of development of encephalopathy there was no statistically significant difference in group A and group B as shown in table 1.

Regarding investigation Total Bilirubin was 7.9±5.2 mg/dl in group A and 7.9±4.5 mg/dl in group B, AST was 1360.4±540.2 in group A and 1405.6±467.6, ALT was 1401.9±612.0 in group A and 1446.2±526.8 in group B, Prothrombin Time (PT) was 50.8±9.4 in group A and 54.7±7.1 in group B, Albumin was 2.744±0.333 in group A and 2.650±0.398 in group B, Serum potassium (mEq/L) was 3.818±0.616 in group A and 3.85±0.636 in group B, Serum creatinine (mg/dl) was 1.031±0.707 in group A and 1.2±0.791in group B and Platelets (per microliter) was 224812±123933 in group A and 203937±151614 in group B,. All the values are indicating mean ± standard deviation and P value shows no statistically significant difference in both the groups except PT as clear from table 1.

Length of hospital stay in group A was 14.4±6.7 days (median 15.5, IQR(11): 7.5days to 18.5days) while in group B it was 23.8±4.1days (median 24, IQR(8): 19.5days to 27.5days) p-value 0.001 as shown in table 2.

Overall mortality was found 43.8% (14 expired out of 32 patients).

Survival status of both groups was compared to see the effect of treatment. In group A 11(69%) patients survived and in group B 7(44%) patients survived. Survival was higher in those who received NAC 11(69%) than those who did not receive NAC 7(44%) but there was no statistically significant difference from evidence shown in table 3.

Discussion

Acute liver failure of various etiologies is not a rare clinical syndrome resulting in sudden necrosis of hepatocytes causing encephalopathy and coagulopathy. Viral hepatitis is reported as the most frequent etiology of acute liver failure from developing countries. Advancement in critical care have

Table 1: Demographic, Etiology, Clinical features and investigations in both groups A & B

	Child with NAC in treatment	Child without NAC in treatment	P–Value	C. I.
Age (Mean ±SD)	7.5±1.366	7.6±1.232	0.615	(-0.644, 0.394)
Male	10	12	0.4456	
Etiologies of ALF			total	percentage
HAV	10	13	23	71.9
Non A-E	3	2	5	15.6
HBV	2	1	3	9.4
Co infection HAV & HEV	1	0	1	3.1
CLINICAL FEATURES				
Fever	10 (31.3)	11 (34.4)		
Loss of appetite	12 (37.5)	13 (40.6)		
Nausea & Vomiting	12 (37.5)	13 (40.6)		
Abdominal Pain	8 (25)	6 (18.8)		
Jaundice	13 (40.6)	16 (50.0)		
Hepatomegaly	11 (34.4)	12 (37.5)		
Bleeding Manifestation	5 (15.6)	5 (15.6)		
HEPATIC ENCEPHALOPATHY				
I	5 (15.6)	6 (18.7)	0.709	
II	7 (22)	4 (12.5)		
III	3 (9.4)	4 (12.5)		
IV	1 (3.1)	2 (6.2)		
ONSET OF ENCHEPHALOPATHY AFTER ONSET OF INITIAL SYMPTOMS				
< 7 Days (hyperacute)	7	5	0.4652	
INVESTIGATIONS				
Total Bilirubin (mg/dl)	7.9±5.2	7.9±4.5	0.892	(-1.352, 1.540)
Direct Bilirubin (mg/dl)	6.1±4.3	6.6±4.2	0.334	(-1.470, 0.532)
AST	1360.4±540.2	1405.6±467.6	0.422	(-162.2, 71.7)
ALT	1401.9±612.0	1446.2±526.8	0.442	(-163.6, 75.1)
Prothrombin Time	55.00±14.41	61.56±14.21	0.2779	(-18.98, 5.86)
Albumin	2.744±0.333	2.650±0.398	0.5636	(-0.245,0.432)
Serum Potassium (mEq/L)	3.819±0.617	3.85±0.637	0.908	(-0.599,0.537)
Serum Creatinine (mg/dl)	0.969±0.679	1.2±0.792	0.419	(-0.824,0.361)
Platelets (/ul)	224813±123934	203938±151615	0.701	(-92815,134565)

Table 2: Comparison Of Groups For Length Of Hospital Stay

Parameters	Mean ±SD	P-value	95% C.I
Group A	14.4±6.7	0.001	(-14.00, -4.75)
Group B	23.8±4.1		

improved overall outcome of ALF, however in advanced cases the definitive therapy is liver transplantation.[16] In our country the liver transplantation facility is not easily available. Rapidly progressive course and associated high mortality of ALF of viral etiology in previously normal children demand alternative treatment. If the cause of ALF is acetaminophen NAC should be administered as soon as possible. But in a study retrospective review of medical records of 170 children presenting with non-acetaminophen induced ALF between 1989 and 2004 was

Table 3: Treatment Groups & Discharge disposition

Group	Survival		Total	d.f	Chi-Square	P-Value
	Yes	No				
A	11	5	16			
B	7	9	16	1	2.03	0.154
Total	18	14	32			

undertaken who were given NAC, which showed decrease hospital stay and better survival in these patients. Although the short comings of the study was it was uncontrolled, retrospective and on a small number of patients.[10]

In a prospective, double-blind trial total of 173 adult patients received NAC (n=81) or placebo (n=92), 20% of patients were of viral etiology. Overall survival was 70% for patients given NAC and 66% for patients given placebo. Transplant-free survival was significantly better for NAC patients (40%) than for those given placebo (27%). Intravenous NAC generally was well tolerated; only nausea and vomiting occurred significantly more frequently in the NAC group (14% vs 4%).1 We found similar results in our cohort for length of hospital stay. Furthermore, comparison was done in our study to see the effect of treatment group on the survival status. Survival was higher in those who received NAC as compared to those who did not receive NAC treatment for ALF.

Further analysis for survival status according to grade of encephalopathy, we found that all patients with encephalopathy grade 3 & 4 expired in both groups and there was statically significant evidence was found in patients with hepatic encephalopathy grade 1 & 2, that who received NAC had higher survival than Non-NAC group. Similar results were reported by WM Lee *et al* that coma grade 1 & 2 receiving NAC found to have significantly higher survival than coma grade 3 & 4 receiving NAC.[1] Sotelo N found early treatment with NAC is safe and effective alternative treatment for acute liver failure of viral etiology.[14] A study from Pakistan also reported death of all patients with grade 4 coma.[15] Results from above studies indicates that NAC augments recovery in some earlier stages of encephalopathy beyond that perhaps significant irreversible damages to body organ occur that have less response to this drug that may be evaluated in further studies.

The limitation of our study is that it is a single center study on small number of patients. Efficacy of NAC may be further evaluated in studies with focus on early administration in grade 1 & 2 of encephalopathy with randomized controlled trails on larger number of patients.

Conclusion

Most common etiology of ALF was found Hepatitis A. There was no significant difference in overall survival of patients treated with NAC and without NAC. There was a significant improvement in survival observed in patients with early stage of encephalopathy grade 1& 2 treated with N-Acetylcysteine.

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