

Efficacy Of N-Acetylcysteine In Non- Acetaminophen Acute Liver Failure.

Mah Rukh¹, Asjid Jabbar², Yasmin Shaikh³, Abdul Azeem⁴, Ahsan Aslam⁵, Sauda Usmani⁶

¹Department of Medicine, DHQ Hospital, Jhang, Pakistan.

Email ID : mahrukh506@yahoo.com

²MPhil Trainee, Department of Pharmacology, Army Medical College, Rawalpindi, Pakistan.

Email ID : asjidjabbar@hotmail.com

³Associate Professor, Department of Pharmacology, Peoples University of Medical & Health Sciences for Women (PUMHSW), Nawabshah, Pakistan.

⁴Associate Professor, Department of Pharmacology, Watim Medical & Dental College, Rawalpindi, Pakistan.

Email ID : azeemhaseeb079@gmail.com

⁵Assistant Professor, Department of Pharmacology, Indus Medical College, Tando Muhammad Khan, Pakistan.

Email ID : ahsanaslam92@hotmail.co.uk

⁶Associate Professor, Department of Physiology, Pak Red Crescent Medical and Dental College, Lahore, Pakistan.

Email ID : sauda.usmani@gmail.com

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ABSTRACT

Introduction: Acute liver failure (ALF) is a relatively rare, but severe, life-endangering medical emergency. To date, there is no established treatment for non-acetaminophen-induced acute liver failure (NAI-ALF) other than liver transplantation, and little is known about the use of N- acetylcysteine (NAC) in NAI-ALF.

Objective: To determine the efficacy of acetylcysteine in non-acetaminophen acute liver failure.

Study Design: Descriptive case series.

Setting: Department of Medicine, Mayo Hospital, Lahore.

Duration of Study: Study was carried out over a period of six months from 03-10-2021 to 03- 04-2022.

Material and Methods: Total 81 patients presented to the Department of Medicine, Mayo Hospital, Lahore, fulfilling the Inclusion criteria were selected. Informed consent was taken from each patient. All patients were given intravenous N- acetylcysteine (150mg/kg in 5% dextrose in 15 mins followed by 50mg/kg over 4 hours then 100mg/kg over 16 hours) for duration of 72 hours. All patients were followed by the researcher for 4 weeks and efficacy and analyzed in SPSS version 25.0 and presented as frequency and percentages.

Results: Total of 81 patients were included in the study, there were 66.7 %(n=54) were in age group of 20-40 years and 33.3% (n=27) were in age group of 41-70 years and mean age was calculated as 737.93±11.09 years. Gender distribution of the patients was done, it showed that 44.4 %(n=36) were male whereas 55.6% (n=45) were females. Percentage of efficacy of acetylcysteine in non- acetaminophen acute liver failure was 30.9%(n=25).

Conclusion: We concluded that in patients with non-acetaminophen-related acute liver failure, acetylcysteine significantly improves overall survival

Keyword: Acute liver failure, Acetylcysteine, Efficacy

1. INTRODUCTION

Acute liver failure (ALF) is an infrequent critical condition that is associated with considerable mortality when it arises in patients with no pre-existing liver diseases [1]. Many different expressions have been used to refer to ALF, such as fulminant hepatic failure, hepatic necrosis, and fulminant hepatitis. In the developed countries, the ALF incidence is 1–6 cases per million population, while in the developing countries, with an abundance of viral hepatitis, it is probably much higher [2]. With the introduction of liver transplantation, survival rates of ALF greatly increased in the developed world to over 65% [3]. In contrast, in the developing world, where optimal medical care and liver transplantation are limited, survival rates are

still considerably poor, at around 50% [4].

While liver transplantation is still the only definitive therapy, supportive care works for most patients and is appropriate for patients with ALF who are able to undergo supportive care while the liver cells regenerate [5]. The effect of liver transplantation on the survival of patients with acute liver failure (ALF) has been profound, although the procedure is still costly and only offered in a few centers [6]. The earlier literature focused on the potential benefits of N-acetylcysteine (NAC) on acetaminophen (paracetamol)-induced ALF, and its long-overdue potential on non-acetaminophen-induced ALF (NAI-ALF) was suggested in the more recent literature due to its multiple, albeit poorly understood, mechanisms of action [6,7]. One study cited an efficacy of 70% for acetylcysteine in the management of non-acetaminophen acute liver failure [8].

The objective of the present study is to examine the evidence for NAC in the management of non-acetaminophen acute liver failure, including the time to liver function test results normalization, and the evidence for postulated efficacy. NAC has long been proven as safe and effective in the management of paracetamol-induced liver injury. The recent shift in research towards looking beyond acetaminophen (paracetamol) towards NAC in non-acetaminophen acute liver failure is of the utmost importance in determining if NAC is a viable treatment option for this condition. The outcomes of this research study will provide the evidence needed for NAC in non-acetaminophen acute liver failure to be considered in decision making by policy makers, health care practitioners, and researchers.

2. SUBJECTS AND METHODS:

From October 2021 to April 2022, a descriptive case series was carried out at the Department of Medicine, Mayo Hospital, Lahore. Based on a 70.0% efficacy level of acetylcysteine in non-acetaminophen acute liver failure, the sample size was estimated to be 81 at 95% confidence level and 10% margin of error. Through non-probability consecutive sampling, all non-acetaminophen drug induced acute liver failure, acute viral hepatitis of disease duration of <8 weeks and 20-70 years of age of either gender were included. Non-acetaminophen acute liver failure was defined as the presence of bilirubin, ALT, AST, INR levels, and hepatic encephalopathy of >5 mg/dl, > 500 U/L, >500 U/L and >2 respectively at presentation and encephalopathy of any degree caused by illness of duration <8 weeks. Efficacy was defined as the reduction in bilirubin, ALT, AST and INR levels by >50% from baseline after 4 weeks of treatment. Patients with a history of right sided heart failure, autoimmune ALF, acute on chronic liver failure, ALF during pregnancy and hepatic shock were excluded from the study. Institutional ethical review committee approval was obtained. A total of 81 patients who presented to the Department of Medicine, Mayo Hospital, Lahore, and met the Inclusion criteria were selected. Informed consent was obtained from all patients.

Patients were administered intravenous N-acetylcysteine therapy in accordance with the specified protocol provided. During the 72 hours of N-acetylcysteine therapy, the researcher's follow up consisted of 4 weeks in which the efficacy (yes/no) was noted as detailed in the operational definition. All of this information (demographics, duration of disease, bmi, urban/rural, efficacy) was captured in a pre-established proforma. The data was analyzed with SPSS 25.0. The quantitative variables (included age, duration of disease, height, weight, bmi, total bilirubin, ALT, AST, INR baseline, INR post-therapy) were summarized with mean and standard deviation. The qualitative variables (included gender, urban/rural status and efficacy) were summarized with frequency and percentage. The paired t test was used to compare the pre- and post-therapy biochemical profile and baseline stratification variables (age, gender, duration of disease, bmi, child Pugh classification, urban/rural) were used to control and post stratification chi square was used to analyze efficacy. P-value ≤ 0.05 was considered as statistically significant.

Table no. 1 Demographic and clinical profile of subjects:

Variables n= 81	Frequency	Percent
Age Mean $\pm$ SD = 37.93$\pm$11.09 years		
20-40	54	66.7
41-70	27	33.3
Gender		

Male	36	44.4
Female	45	55.6
Residential status		
Rural	25	30.9
Urban	56	69.1
Duration of disease(weeks) Mean =5.02±1.21		
1-4 weeks	13	16.0
5-7 weeks	68	84.0
BMI Mean =25.35±1.83		
17-25 kg/m ²	43	53.0
>25 kg/m ²	38	47.0
Efficacy		
Yes	25	30.9
No	56	69.1

Table no. 2: Biochemical profile of subjects before and after intervention:

Variable n= 81	Before (mean ±SD)	After (mean ± SD)	P values (paired t test)
Bilirubin (mg/dl)	7.02±2.21	3.24±1.20	0.000
ALT(U/L)	655.23±63.50	320.20±30.20	0.000
AST(U/L)	721.32±65.30	330.40±31.20	0.000
INR	3.25±0.65	1.20±0.20	0.000

Table no. 3: Stratification for efficacy with age, gender duration of disease BMI and child pugs classification

Variables n = 81	Efficacy		Total	P-value
	Yes	No		

Age group	20-40 years	14	40	54	0.174
		25.9%	74.1%	100.0%	
	41-70 years	11	16	27	
		40.7%	59.3%	100.0%	
Gender	Male	10	26	36	0.591
		27.8%	72.2%	100.0%	
	Female	15	30	45	
		33.3%	66.7%	100.0%	
Duration of disease	1-4 weeks	46.2%	53.8%	100.0%	0.193
		19	49	68	
	5-7 weeks	27.9%	72.1%	100.0%	
BMI group	17-25 kg/m2	16	27	43	0.188
		37.2%	62.8%	100.0%	
	>25 kg/m2	9	29	38	
		23.7%	76.3%	100.0%	
Child pugh class	child class A	8	8	16	0.137
		50.0%	50.0%	100.0%	
	child class B	16	47	63	
		25.4%	74.6%	100.0%	
	child class C	1	1	2	
		50.0%	50.0%	100.0%	
Residential status	Rural	16	9	25	0.001
		64.0%	36.0%	100.0%	
	Urban	9	47	56	
		16.1%	83.9%	100.0%	

3. RESULTS:

Table 1 outlines the demographic and clinical characteristics of the 81 study participants. The participants' average age was 37.93 years, with a standard deviation of 11.09 years. The participants were predominantly younger, as 66.7% were 20-40 years of age. The sample was equally distributed with 44.4% of the respondents being male and 55.6% being female. Most of the study participants 69.1% were from urban regions, while 30.9% were from rural regions. Approximately 84% of the participants had a disease duration of 5-7 weeks, the average duration being 5.02 weeks. In regards to the body mass index (BMI) of the participants, 53% were within the range of 17-25 kg/m² and 47% exceeded 25 kg/m². In terms of treatment outcome, 30.9% had treatment response compared to 69.1% with no treatment response.

Table 2 outlines participants' biochemistry and their changes from pre to post intervention. Key indicators showed positive

changes and all improvements were statistically significant. Bilirubin levels reduced from 7.02 mg/dl to 3.24 mg/dl ($p < 0.001$), ALT levels from 655.23 U/L to 320.20 U/L ($p < 0.001$), AST levels from 721.32 U/L to 330.40 U/L ($p < 0.001$), and INR from 3.25 to 1.20 ($p < 0.001$).

Table 3 presents the relevant stratification analysis for efficacy based on age, gender, length of the disease, BMI, Child Pugh classification, and residential status. The results indicate that residential status had a considerable effect on treatment efficacy ($p = 0.001$), with greater efficacy noted among participants from rural areas. No considerable relationships were observed in the variables of age, gender, length of the disease, BMI, or Child Pugh class. This shows the relevance of residential status on the success of the intervention.

4. DISCUSSION:

Acute liver failure (ALF) is the decline in liver function in days to weeks in individuals without liver disease. Primary causes of ALF are viral infections (especially hepatitis) and hepatotoxic medications (especially acetaminophen). Unlike chronic liver failure, which undergoes gradual deterioration, ALF can result in rapid and extreme deterioration (e.g., cerebral edema, bleeding) that demands immediate attention. ALF can be classified into hyper-acute, acute, and sub-acute forms, the first two encompassing the concept of fulminant hepatic failure. Both hyper-acute and acute forms closely inform the cause and forecast of ALF. Interestingly, patients with HE that develops in the first 8 weeks of symptom onset are predicted to survive longer, while patients with a more gradual symptom onset are more likely to die. Again, this principle is most commonly observed with liver encephalopathy. The leading causes of death in ALF are multiorgan failure (more than 50%), intracranial hypertension (ICH), and infections.

Age demographics for the 81 patients indicate that the largest proportion, 66.7%, fell within the 20-40 year age range, with the remaining 33.3% in the 41-70 year age category. The average age for study subjects was 37.93 ± 11.09 years. Gender demographics indicated that 44.4% of the patients were men, and 55.6% were women. The reported efficacy of N-acetylcysteine (NAC) for therapeutic care of non-acetaminophen-induced acute liver failure (NAI-ALF) was 30.9% ($n=25$), which aligns with the previously reported NAI-ALF studies [6, 7].

Numerous studies describe the positive outcomes of using NAC to mitigate acetaminophen-induced acute liver failure (ALF). Recently NAC has been used to treat nonacetaminophen-induced acute liver failure (NAI-ALF) as well. It was reported that in a study NAC was effective in 70% of NAI-ALF [8] cases. Initially, in the early 1980's, acute hepatitis B (HBV) was the leadest cause of ALF. However, within the las 30 years, toxic agents especially acetaminophen has become the leading cause in the majority of developed countries. Acetaminophen poisoning accounts for 40% of ALF cases in the USA [12], UK [19], and Scandanavia [13, 14] and viral hepatitis accounts for 10% of the cases. Conversely, Southern Europe, Africa, and Asia have a greater excess of hepatotropic viruses especially HBV which accounts for 40% of the ALF cases in the Mediterranean region while toxicity foes for 20% [15]. In Germany, ALF cases are estimated from 200-500 per year as per the transplantation and hepatology centers, and there are not many well designed studies on the region's epidemiology. It appears that the weaker sex is afflicted more ofthen as recent studies show a male to female ratio of 52% to 63% [16].

A review of the records of ALF patients at Hannover Medical School showed that for 102 patients, the most frequent cause of ALF was unknown (21%), followed by acetaminophen toxicity (16%) and acute HBV infection (18%) [17]. Findings of the larger retrospective study of 134 ALF patients were even more striking: 39% of ALF cases were due to toxicity, mainly acetaminophen, and 23% were due to infections of the liver with ALF-related viruses [18]. These findings suggest that acetaminophen and other toxic agents are becoming more important ALF causes in developed countries.

In the context of ALF, hepatic encephalopathy (HE) is a pivotal clinical feature, varying from mild abnormalities of the higher cortical functions such as alterations of mood and the ability to concentrate (grade I) to profound coma (grade IV). Patients in the acute or hyper-acute phases of liver failure are the most likely to develop grade IV encephalopathy and are at risk of developing cerebral edema. However, the most recognisable signs of elevated intracranial pressure, such as papilledema or a fixed and dilated pupil, are less reliable signs and develop late in the course of the disease. Although CT scans of the head are routinely obtained when intracranial bleeding is a consideration, they provide little value in the early detection of cerebral edema, which is an important marker of the progression of ALF. In these circumstances, subdural methods of invasive intracranial pressure monitoring are advised, although their expected fatal hemorrhage risk of ~1% poses a relative contraindication that must be assessed against the expected value of the information to be gained [20].

Patented in 1960, N-acetylcysteine (NAC), sulfhydryl containing, mucolytic compound, has been used since 1967 for acetaminophen overdose, and later for cystic fibrosis and chronic obstructive pulmonary disease (COPD). NAC is now being utilized for its mucolytic, anti-inflammatory, and potent free radical scavenging characteristics in the management of non-acetaminophen-induced ALF. NAC protects cells against oxidative damage by replenishing glutathione. NAC has a 6.25 hour half-life and is poorly absorbed, with an oral bioavailability of only 4-9.1%, which may explain the lack of clinical effects at the recommended daily doses of 1200 mg or less. Nausea, vomiting, and diarrhea are common side effects. Furthermore, NAC has protective effects against oxidative damage to cells, which may have health implications considering the cysteine deficiency associated with aging, notably sarcopenia [22].

5. CONCLUSION:

To conclude, acute liver failure (ALF) continues to be a potentially fatal condition with a considerable mortality rate. In developed countries, the growing impact of acetaminophen overdose on ALF emphasizes the necessity for prompt diagnosis and treatment, of which N-acetylcysteine (NAC) will always be the most effective drug for acetaminophen-related ALF. Future studies should evaluate the use of NAC for the treatment of non-acetaminophen-related ALF and potential use for complicated hepatic encephalopathy and cerebral edema.

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