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Original Research Article

Continuous Intravenous N- Acetylcysteine in iNon Acetaminophen Acute Liver Failure In Children

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Abstract

Introduction: Assessing How Long-Term Intravenous N-Acetylcysteine Infusions Can Improve a Child's Non-Acetaminophen Acute Liver Failure (Nai-Alf) Outcomes.

Material and Methods: A predesigned proforma is used to conduct this observational research. N-acetylcysteine at a dosage of 150 mg/kg/day in 3 split doses by continuous intravenous infusion for up to 7 consecutive days was given to 41 instances with non-acetaminophen caused acute liver failure in the age group of 3 months to 14 years who came to VIMSAR's OPD & IPD, Burla. From the hospital registry, 37 patients were chosen that did not receive N-acetylcysteine and had acute liver failure not caused by acetaminophen. Software called SPSS16v was used to analyse all of the data.

Results: When compared to patients who did not receive NAC, those who had lower grades of hepatic encephalopathy (HE I & HE II) showed a reduction in the length of their ICU stay as well as an earlier recovery in their liver function. In patients presenting with grades III or IV hepatic encephalopathy, NAC was found to be ineffective in reducing hospital stays or ICU deaths. NAC use in youngsters has been determined to be safe.

Conclusion: The current study's safety profile suggests that intravenous NAC should be investigated for patients with early stage NAI-PALF. Nevertheless, further research is required to identify response predictors and the ideal dosage and duration of NAC treatment.

Keywords: Abrupt Liver Failure Caused By Non-Acetaminophen, Hepatic Encephalopathy Caused By N-Acetylcysteine.

Introduction

A terrible illness known as paediatric acute liver failure (PALF) occurs when previously healthy children with a normal liver quickly experience liver damage and hepatic function impairment from a variety of sources, leading to catastrophic illness in a matter of days.

It is a very uncommon yet serious, multisystemic emergency that poses a serious risk to life and frequently results in death in youngsters. In the US, acute liver failure occurs in around 17 instances per 100,000 people annually across all age categories; the prevalence in the paediatric age group is unknown**.** Ninety to ninety-five percent of cases in India are attributed to viral hepatitis According to several studies, hepatotropic viruses account for 42% to 85% of cases, whereas individuals with clinical presentations suggestive of viral hepatitis but without a detectable viral marker make for 15% to 47% of cases.

One of the most common aetiologies (23–41% of cases) is still hepatitis A. ALF instances are significantly influenced by acute hepatitis B infection (11–27%). In India, paracetamol has been linked to ALF in relatively few cases.

Conversely, the most frequent cause of ALF in western nations is paracetamol (30–35% in the USA and 60% in Europe). Since the majority of PALF cases lack a known aetiology, research on the process by which hepatocytes are destroyed has not been possible even when the aetiology of PALF is understood, the mechanism is still unclear Other than liver transplantation, and there is no recognised therapy for acute liver failure not caused by paracetamol.

The majority of the time, supportive care is used, unless there are certain disorders, including acute paracetamol toxicity, herpes virus, Wilson disease, or autoimmune hepatitis that might benefit from tailored therapy.

Improved survival in paediatric acute liver failure is linked to early referral to a liver transplantation clinic, advancements in medical care, and liver transplantation. With intensive treatment, the death rate from PALF can range from 60 to 80%, indicating a dire outlook Ten to fifteen percent of paediatric liver transplants carried out in the US each year are PALF

The need to find a therapy for increased survival stems from the poor long-term results of liver transplantation for PALF when compared to other indications for LTX.N-acetyl cysteine (NAC) is the preferred therapy for acute acetaminophen toxicity because it restores mitochondrial and cytosolic glutathione levels and aids in the excretion of N-acetyl-p-benzoquinone-imine (NAPBQI), a toxic metabolite of acetaminophen.

Research further reveals that NAC functions as a vasodilator to enhance 02 deliveries, strengthens antioxidant defence, and scavenges free radicals Since NAC has been used to treat acute acetaminophen toxicity; it is being gradually included to treatment plans for paediatric acute liver failures that do not involve acetaminophen, regardless of the underlying cause, at a number of paediatric centres worldwide.

Material and Methods

Study Subjects (Inclusion Criteria):

1. Children with NAI-ALF who are 3 months to 14 years old
2. Biochemical proof of recent liver damage
3. Hepatic encephalopathy shown clinically
4. Biochemical proof of coagulopathy (INR > 1.5 after Vit K correction along with hepatic encephalopathy or > 2 after Vit K correction combined with encephalopathy)

Study Subjects (Exclusion Criteria):

1. Chronic liver disorders are present
2. Based on Rumack-Matthew nomograms, there may be acute paracetamol poisoning.
3. Past history of NAC exposure during the current illness
4. The existence of cancer
5. The existence of cerebral herniation symptoms
6. The existence of intractable hypotension, which is characterised by a systolic blood pressure of less than 85 mmHg, or hypotension that necessitated the use of inotropic medications in addition to dopamine renal dosage.

All patients who meet the inclusion criteria and are hospitalised to the paediatrics department at VIMSAR, Burla between November 2014 and October 2016 will be studied in the NAC group, meaning they will receive continuous IV NAC infusions for a maximum of seven days. The control group will be chosen from hospital records of patients who meet the inclusion criteria (historical controls) and who, between October 2012 and October 2014, had not received N-acetylcysteine (NAC). Due to the fact that the death rate in NAI-ALF without liver transplantation ranged from 74% to 88%, I used 84% for mortality with supportive treatment (historical control group) for calculating the sample size. At a 5% level of significance and 80% research power, the sample size determined for the NAC group was 41 patients in each arm, based on the 75% death rate reported in the earlier NAI-ALF trial employing NAC. It was a two-sided P value.

The investigation was conducted from November 2014 to October 2016 in the paediatric department of VIMSAR, Burla.

Case selection (NAC group): All children who met the inclusion and exclusion criteria and presented with acute liver failure not caused by acetaminophen throughout the designated research period were considered cases and received continuous intravenous N-acetylcysteine therapy.

Selection of controls (non-NAC group): During the period from October 2012 to October 2014, controls who met the inclusion and exclusion criteria and were hospitalised for acute liver failure not caused by acetaminophen will be chosen from hospital records.

They will also not have taken N-acetylcysteine (NAC). A variety of baseline clinical and biochemical indicators were collected in both groups after patients and controls were chosen and consents were obtained. Every patient chosen as a case received care in the PICU.

Prodromal symptoms, jaundice, altered sensorium and severity of hepatic encephalopathy, convulsion, hepatomegaly, splenomegaly, oligouria, clinical ascites, and bleeding manifestations were among the clinical parameters noted. Any additional hepatotoxic drug intake, including the use of

homoeopathic and herbal remedies as well as mushrooms, was also recorded in the patient's medical history.

Seven to fourteen days before the onset of jaundice, prodromal symptoms include fever, anorexia, nausea, vomiting, and malaise.

Result:

13 individuals discontinued the research midway because they were sent to a higher facility or requested an early release.

A total of 54 participants were enrolled for the study (NAC group) between November 2014 and October 2016. 37 patients' personal information could be discovered out of the 43 patients who were determined to meet the inclusion criteria in the control group.

Table 1: No of Participants in Each Group:

	NAC group	Non-NAC group
Total no of enrolled cases	54	43
Cases actually studied	41 (75.9 %)	37 (86.04 %)
Cases left mid-way	13 (24.07 %)	6 (13.9 %)

Table 2: Age Distribution in Each Group:

Age groups	NAC group (41)	Non-NAC group (37)
< 1 yr	0	1 (2.7 %)
1-3 yrs	4 (9.7 %)	5 (13.5 %)
4-6 yrs	15 (36.5 %)	9 (24.3 %)
7-9 yrs	10 (24.3 %)	14 (37.8 %)
> 10 yrs	12 (29.2 %)	8 (21.6 %)

Table 2 shows age distribution in each group. Maximum participants were in 4-6 yrs age group (15) in NAC group while maximum participants were (14) in 7-9 yrs age group in Non-NAC group.

Table 3: Sex Distribution in Each Group

Sex	NAC group (41)	Non-NAC group (37)
Male	25 (60.9 %)	21 (56.7 %)
Female	16 (39.1 %)	16 (43.2 %)

Table 3 shows sex distribution in each group. NAC group consisted of 25 male children & 16 female children while Non-NAC group consisted of 21 male children & 16 female children.

Table 4: Common Clinical Presentation:

Sl. No	Clinical presentation	NAC group (41)	Non-NAC group (37)
1	Prodromal symptoms	33 (80.4 %)	27 (72.9 %)
2	Fever at presentation	5 (12.1 %)	7 (18.9 %)
3	Jaundice at presentation	41 (100 %)	37 (100 %)
4	Altered sensorium	41 (100 %)	37 (100 %)
5	Convulsion	8 (19.5 %)	11 (29.7 %)
5	Reduced urination	14 (34.1 %)	8 (21.6 %)
6	Hepatomegaly	33 (80.4 %)	30 (81 %)
7	Splenomegaly	3 (7.3 %)	4 (10.8 %)
8	Ascites	20 (48.7 %)	15 (40.5 %)
9	Bleeding manifestation	19 (46.3 %)	13 (35.13 %)

The typical ways that patients with NAI-ALF present are displayed in Table 8. Although jaundice and altered sensorium were observed in all patients in both groups, other symptoms and indicators varied. Prodromal symptoms were observed in 72.9% of cases in the non-NAC group and 80.4% of cases in the NAC group. Hepatomegaly was observed in 33 out of 41 instances (80.4%) in the NAC group, but in 30 out of 37 cases (81.1%) in the Non-NAC group. Petechiae, purpura, and bleeding from the IV line insertion site were among the overt bleeding signs observed in 13 patients (35.13%) and 19 patients (46.3%) in the Non-NAC group.

Table 5: Distribution of Cases According to the Grading of Hepatic Encephalopathy (He)

HE grade	NAC group (41)	Non-NAC group (37)
I	5 (12%)	6 (16.2%)
II	8 (19.5%)	7 (18.9%)
III	12 (29.2%)	10 (27 %)
IV	16 (39 %)	14 (37.8 %)

Table 5 lists the number of instances in each group for each degree of hepatic encephalopathy. The majority of patients in both groups presented with HE grade IV, indicating both a late hospital admission and a fast development of the illness. Only 13% of patients in the NAC group and 16.2% of cases in the Non-NAC group had Grade I hepatic encephalopathy, compared to 39% of cases in the NAC group and 378.8% of cases in the Non-NAC group.

Table 6: Common Etiology Observed Causing Nai-Palf

Etiology	NAC group (41)	Non-NAC group (37)
HAV	11(26.8 %)	14 (37.8 %)
HEV	12 (29.2 %)	5 (13.5 %)
Malarial	3 (7.3 %)	4 (10.8 %)
Drug/toxin/herb	3 (7.3 %)	2 (5.4 %)
Idiopathic	14 (34.1 %)	12 (32.4 %)

Table 6 the prevalent aetiology of NAI-PALF found throughout the investigation is displayed in A greater number of HEV cases were seen throughout the research period, which is consistent with the epidemic that occurred in the Sambalpur area between December 2014 and March 2015, even though many cases in both groups had unclear or idiopathic causes. Overall, the NAC group was dominated by idiopathic cases (34.1%), whereas the non-NAC group was dominated by HAV-related PALF (37.8%). Only three instances (7.3%) in the NAC group—two valproate cases and one toxic herb case—presented with drug-toxin-herb-induced hepatotoxicity, whereas two cases—one connected to mushrooms and one valproate case—in the Non-NAC group showed signs of drug-toxin-induced hepatotoxicity.

Discussion

In children, PALF is a very uncommon but serious, potentially deadly, multisystemic emergency. A liver transplant is the only recognised therapy for acute liver failure without paracetamol. Because of its anti-oxidant and vasodilatory qualities, N-acetylcysteine—which is mainly used as an antidote in acetaminophen-induced acute liver failure (ALF)—is also useful in lowering mortality and liver transplantation free survival in non-acetaminophen-induced acute liver failure (NAI-ALF)? The current study looked at whether NAC can lower hospital stays and death in children with NAI-ALF in a setting lacking a liver transplant centre. For a maximum of seven days, children diagnosed with NAI-ALF received a continuous intravenous infusion of NAC at a rate of 150 mg/kg/day. The target sample size of 41 was determined at a 5% level of significance and 80% study power, based on prior research that showed 75% of deaths were caused by NAI-ALF. During the period of November 2014 to October 2016, a total of 54 individuals were enrolled for the trial (NAC group); 13 of these patients withdrew from the study midway owing to requests for early discharge or referrals to higher centres. Out of the 43 patients who met the inclusion criteria for the control group, 37 patients' personal information could be located (table 5).

A large majority of clinical and biochemical indicators were similar across the two groups. The two groups showed no statistically significant differences in terms of age, gender, coma degree, or biochemical markers of liver impairment. Research by Mumtaz et al. and Squires et al. also revealed comparable clinical and biochemical characteristics across the two groups. Table 7 indicates that 56.7% of patients in the Non-NAC group and 60.9% of patients in the NAC group were men. Table 6 indicates that the highest percentage of patients in the NAC group were in the 4-6 year age group (36.5%), whereas the highest percentage of patients in the Non-NAC group were in the 7-9 year age group (37.8%).

In the NAC group, not a single patient was determined to be younger than one year, but in the majority of patients in both cohorts had jaundice and altered sensorium (tables 8 and 10); further symptoms and indicators varied. Prodromal symptoms were observed in 82.4% of NAC group patients compared to 72.9% of non-NAC group cases. In the Non-NAC group, hepatomegaly was identified in 30/37 instances (81.1%), whereas it was reported in 33/41 cases (80.4%) in the NAC group.

In the NAC group, 19 patients (46.3%) and in the non-NAC group, 13 patients (35.13%) had overt bleeding signs such as purpura, petechiae, and

bleeding at the IV line insertion site. Convulsion upon presentation was an unusual presentation that was observed in 29.7% of patients in the Non-NAC group and 19.5% of patients in the NAC group. Prodromal symptoms were observed in 72.9% of patients in the Non-NAC group and 80.4% of patients in the NAC group.

In individuals with malarial hepatopathy, splenomegaly was more prevalent (table 8 & 10). Acute liver failure caused by drug or toxin-related hepatotoxicity was rare in both groups, with valproate-induced hepatic failure being the most frequent cause. According to Table 9, the most common kind of encephalopathy in both groups was grade IV hepatic encephalopathy (39.8% instances in the NAC group and 37.8% cases in the Non-NAC group). When the cases were first presented, the majority of patients in both groups (68% in the Non-NAC group and 64.8% in the NAC group) showed higher degrees of encephalopathy (grades III & IV).

Patients with Grade III and IV hepatic encephalopathy were shown to have a lower frequency of hepatomegaly, although both groups had similar rates of ascites, bleeding symptoms, profound jaundice, and characteristics of elevated ICP. As shown in the figure, the most prevalent aetiology of NAI-PALF in the Non-NAC group was HAV (37.8%), followed by idiopathic cases (32.4%), while the major aetiology in the NAC group was found to be idiopathic (34.1%), followed by HEV (29.2%). According to the study conducted by Squires R H et al., there was no significant difference in the distribution of final diagnoses between the two groups.

In the Squires et al. research, idiopathic causes were likewise the most prevalent. Between January and July 2015, there was an increase in the number of HEV cases in the NAC group, which was in line with the HEV pandemic in the Sambalpur region. In the third-world nation where waterborne illnesses are prevalent, acute HEV infection is frequently observed.

Conclusion

Compared to patients who did not receive NAC, patients who had lower degrees of hepatic encephalopathy (HE I & HE II) upon presentation showed a reduction in the amount of time spent in the intensive care unit. Compared to patients who did not receive NAC, those who had lower degrees of hepatic encephalopathy at presentation and had taken NAC exhibited considerably quicker improvements in liver function tests.Research indicates that youngsters can safely use NAC.In patients with hepatic encephalopathy grades III or IV, NAC was not proven to be helpful in reducing ICU/hospital stay or decreasing death. It was discovered that the non-existence of hepatomegaly, INR >1.9, hypoglycemia, Ionotrope demand, and need for a mechanical ventilator were the independent prognostic variables that predicted death.

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