

Use of N-Acetylcysteine in Children with Fulminant Hepatic Failure Caused by Acute Viral Hepatitis

Ali Faisal Saleem, Qalab Abbas and Anwar ul Haque

ABSTRACT

Objective: To determine the efficacy of N-acetylcysteine (NAC) in children aged > 1 month to 16 years admitted with Fulminant Hepatic Failure (FHF) secondary to Acute Viral Hepatitis (AVH) in a tertiary care center of a developing country.

Study Design: Analytical study.

Place and Duration of Study: Department of Paediatrics, The Aga Khan University Hospital, Karachi, Pakistan, from January 2007 to December 2011.

Methodology: Medical records of children (> 1 month - 16 years) with FHF admitted with AVH of known etiology who received NAC were reviewed retrospectively. Liver function tests (mean \pm SD) at baseline, 24 hours after NAC and before or at the time of discharge/death were recorded and compared via using repeated measures ANOVA (r-ANOVA). Efficacy of NAC is defined in improvement in biochemical markers, liver function test and discharge disposition (survived or died). Mortality associated risk factors were identified by using logistic regression analysis. P-value and 95% confidence interval were recorded.

Results: Forty children (mean age was 80 ± 40 months) with FHF secondary to AVH received NAC. Majority were males (n=25; 63%). Vomiting (75%) and jaundice (65%) were the main presenting symptoms, one-third had hypoglycemic, while 40% had altered sensorium at the time of admission. There was significant statistical difference in liver enzymes and prothrombin time on admission comparing at discharge in children received NAC ($p < 0.001$). Fifteen (38%) children died. Severe vomiting {Odds Ratio (OR) 0.22, 95% Confidence Interval (CI) 0.05 - 0.8}, jaundice (OR 9.3, CI 1.1 - 82.6), inotropic support (OR 20.6, CI 3.5 - 118.3) and mechanical ventilation (OR 4.3, CI 1.1 - 16.6) at the time of admission are associated with risk factors for mortality in children with FHF secondary to AVH.

Conclusion: NAC used in children with FHF secondary to AVH is associated with markedly improved liver function tests and recovery. FHF with complications is high risk for mortality.

Key Words: N-acetylcysteine. Acute viral hepatitis. Fulminant hepatic failure. Children.

INTRODUCTION

Acute viral hepatitis (A and E) is a predominant cause of Fulminant Hepatic Failure (FHF) in developing countries where viral etiology accounts for approximately 74% of the acute FHF.^{1,2} It is a life-threatening and devastating medical emergency in a previously healthy child. Although most of the viral hepatitis is self-resolving and causes milder disease but this could be devastating and lethal. FHF has been classified into hyper acute, acute and sub-acute liver failure on the basis of duration of the disease.³ Almost all children in developing countries has been exposed to hepatitis A by the age of 5 years.⁴ Children who developed FHF secondary to AVH has a high mortality because of unavailability of specific treatment as only supportive management is available which is occasionally effective in such a severe and high

risk disease; whereas only a few patients recover spontaneously.¹ Orthotropic liver transplantation is the best option in management in FHF with a good one and 5-year transplant free survival is 74% and 69% respectively. However, unfortunately this option is either too expensive with donor and experience limitations leading to non-availability all around globe.⁵

Acetaminophen (APAP) is one of the most frequently used analgesics, and is the most commonly used self-poisoning substance leading to FHF in the developed world.^{1,6} The most effective treatment for APAP toxicity is N-acetylcysteine (NAC).⁷ NAC is a glutathione having antioxidant properties that scavenges the free radicals and improves hepatic blood flow via oxygen extraction through its vasodilator property.⁸ Its use in non-acetaminophen induced fulminant hepatic failure is controversial. Some studies showed a beneficial outcome in children who received NAC in Acute Viral Hepatitis (AVH),^{9,10} while other without improvement.^{11,12} Recently, there is a shift of beneficial effects of NAC use in viral etiology induced FHF.¹⁰ The two recent randomized control trials on using NAC in non-APAP toxicity FHF showed some marginal improvement in outcome.^{12,13} Intravenous NAC versus placebo in adults with non-APAP liver failure, NAC did not improve

Department of Paediatrics and Child Health, The Aga Khan University Hospital, Karachi.

Correspondence: Dr. Ali Faisal Saleem, Assistant Professor, Paediatric Infectious Diseases, Department of Paediatrics and Child Health, The Aga Khan University, Stadium Road, Karachi.

E-mail: ali.saleem@aku.edu

Received: February 24, 2014; Accepted: March 30, 2015.

survival at 21 days. However, a sub-analysis of the secondary outcomes revealed improved Liver Transplantation (LTx)-free survival at 3 weeks for those with grade 1 - 2 hepatic encephalopathy.¹³

It is difficult to draw a conclusion of NAC efficacy in children affected by AVH in developing countries by using these two trials because one study was on adults, while the study on children had very few children with AVH. Therefore, it is essential to do study in developing country where the burden of AVH (A and E) associated morbidity remains high,² and liver transplantation facilities are scarce, and available on very high cost.

The aim of this study was to assess the effectiveness in preventing morbidity and mortality in children receiving NAC for AVH induced FHF by measuring the change in their laboratory and clinical parameters before, during and after the NAC and identify the prognostic markers for survival in children receiving NAC for AVH.

METHODOLOGY

The study was conducted at the Paediatric ICU (PICU) of AKUH, Karachi. Medical records of patients aged one-month to 16 years admitted in PICU with diagnosis of FHF during 2007 - 11 were reviewed. Total 40 patients were admitted with diagnosis of FHF secondary to AVH and received NAC. FHF other than viral etiologies were excluded. Data was retrieved from, (i) hospital information system using International Classification of Diseases (ICD-9) acute liver failure/FHF (570.0), hepatic coma (572.2), acute hepatic necrosis (570), and (ii) inpatient paediatric ICU registry. Use of NAC was re-confirmed with the hospital pharmacy data base.

Paediatric acute liver failure study group (PALFSG) definition of fulminant hepatic failure was biochemical evidence of liver injury, no history of known chronic liver disease, coagulopathy not corrected by vitamin K, INR greater than 1.5 with encephalopathy or greater than 2 without encephalopathy.^{5,14,15} NAC was given intravenously as 21-hour regimen in 3 doses with cumulative dose of 300 mg/kg over 21 hours (initial loading dose of 150 mg/kg over one hour, followed by 50 mg/kg for 4 hours, then continuous infusion of 100 mg/kg over next 16 hours).^{16,17} Patients were observed for any sign of anaphylaxis, hypotension and other side effects. Demographic features, presenting complaints, consciousness at the time of arrival (Glasgow Coma Scale - GCS), laboratory and biochemical markers i.e., LFTs, INR blood sugar levels and electrolytes, viral serology (Hepatitis A, E,) were recorded.

Efficacy of NAC is defined in improvement in biochemical markers, liver function test and discharge disposition (survived or died).

The statistical analysis was performed by using SPSS software package (version 20.0, SPSS). Continuous

variables (i.e., age, liver function tests, and electrolytes) were presented in the form of mean, standard deviation and median. Categorical variables (gender, presenting complaints, complications and discharge disposition) were presented in frequency and percentages. Statistical differences in biochemical and laboratory parameters (i.e., presenting complaints, laboratory studies including AST, ALT, bilirubin, PT/INR and albumin) at three point times; (i) at admission, (ii) 24 hours after NAC administration and (iii) before discharge or death were made by repeated measures analysis of variance (ANOVA) comparing to their discharge disposition. Normality assumption was checked for biochemical variables and Friedman's test (non-parametric test for multiple comparisons for repeated measures ANOVA) was used to compare the variables without normal distribution. A p-value < 0.05 was considered significant. Univariate analysis was performed, and chi-square, Odds ratio and p-value for mortality associated risk factors in children with AVH received NAC has been calculated. The study was approved by the University Ethical Review Board (2310-Ped-ERC-12).

RESULTS

Forty children with FHF secondary to AVH received NAC (Figure 1) with mean age of 80 months (median 72 months). Majority of them were males (n=25, 63%). Vomiting (n=30, 75%), jaundice (n=26, 65%), and fever (n=20, 50%) were the major presenting complaints. Eleven children presented with low GCS of 8/15 (n=11, 28%). Baseline serum LFTs at the time of admission were ALT (mean = 2102 IU/L; median = 1497 IU/L), AST (mean = 2495 IU/L; median = 1552 IU/L), Prothrombin time (mean = 45 seconds; median = 30 seconds), INR (mean = 4; median = 3), total bilirubin (mean = 17 mg/dl; median = 11 mg/dl) and albumin (mean = 2.8 gm/L; median = 2.7 gm/L). Mean length of PICU stay was 3.4 ± 2 days (median 3 days) and overall mortality rate was 375 per 1000 children developed FHF secondary to AVH (Table I).

Table II compared the mean change in LFTs at three time points in the children received NAC. A statistically significant improvement in the mean laboratory parameters has been observed in ALT, AST and PT (p = < 0.001). Table III compared the LFTs of children survived with those who died at three different time points (baseline, 24-hour and before discharge or death after NAC administration) by using r-ANOVA. There is reversal of ALT/AST found at three time points in children who died. There is statistically significant differences in LFTs observed over time severely deranged PT (p=0.01), INR (p=0.05) and a high serum bilirubin (SBR) has been observed in children who died (Table III). Jaundice (OR 9.3; CI = 1.1 - 82.6) at presentation, acute kidney injury (OR 3.5; CI = 0.9 -

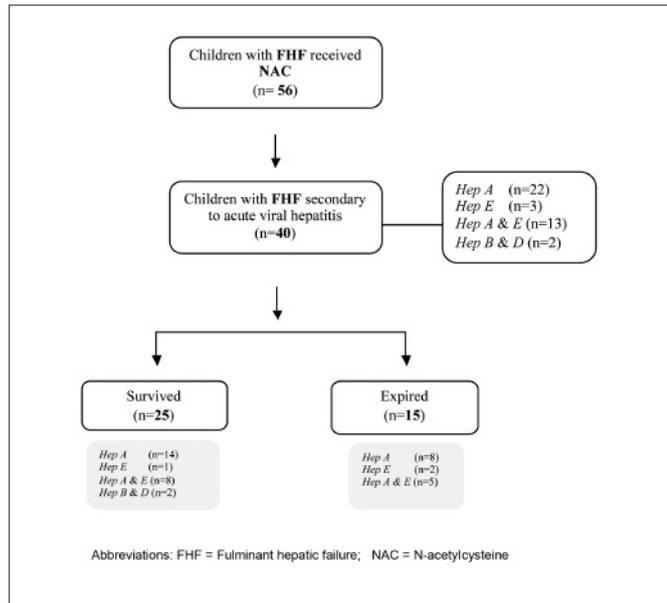


Figure 1: Flow diagram of study.

Table I: Demographic and clinical features of study participants received N-acetylcysteine (n=40).

Variables	N (%)
Age (months) (mean ± SD)	80 ± 40
Male	25 (63)
GCS 8 or less at admission	11 (28)
Presenting symptoms	
Vomiting	30 (75)
Jaundice	26 (65)
Fever	20 (50)
Altered sensorium	16 (40)
Abdominal symptoms	8 (20)
Laboratories at admission	
Liver function test (mean ± SD)	
SGPT (ALT) (n=40)	2102 ± 1509
SGOT (AST) (n=35)	2495 ± 2786
PT (n=40)	45 ± 35
INR (n=40)	4 ± 2.3
SBR (total) (n=40)	17 ± 14
Albumin (n=37)	2.8 ± 0.5
Platelets (n=40) (mean (range))	305 ((24, 1079))
Serum sodium (n=40) (mean ± SD)	133 ± 5
Hypoglycemia*	12 (30)
Positive blood culture	9 (23)
ICU therapy	
Mechanical ventilation	24 (60)
Inotropic support	19 (48)
Renal replacement therapy	5 (13)
Length of ICU stay (days) (mean ± SD)	3.4 ± 2
Complications	
AKI	12 (30)
Grade-IV coma	10 (25)
Bleeding	3 (8)
Discharge disposition	
Died	15 (38)

*Hypoglycemia (random blood sugar of less than 60 mg/dl).
Abbreviations (GCS, Glasgow coma scale; ALT, alanine transaminase; AST, aspartate transaminase; PT, Prothrombin time; INR, international normalization ratio; SBR, serum bilirubin; AKI, acute kidney injury)

Table II: Comparison of changes in liver function test before and after N-acetylcysteine in children with AVH.

	Pre-NAC	24 hours post-NAC	Before discharge/death	p-value [^]
ALT	2101 ± 1529	1019 ± 816	466 ± 495	<0.001*
AST	2500 ± 2005	528 ± 451	435 ± 431	<0.001*
PT	43.5 ± 34	31.2 ± 30	28.3 ± 33	<0.001*
INR	3.8 ± 2	3.3 ± 3	4.7 ± 9	0.51**
SBR	17.6 ± 14	17 ± 12	14.6 ± 11	0.15
Albumin	2.8 ± 0.5	2.9 ± 0.51	2.9 ± 0.5	0.16

[^] Normality assumption for all above variables was checked. "Friedman's test" (Non-parametric test for multiple comparison for repeated measures ANOVA) was used.
*p < 0.001, **p = 0.001 (Friedman's test).

Table III: Comparison of changes in liver function test among children who survived compared to dead after N-acetylcysteine.

		Survived (mean ± SD)	Died (mean ± SD)	p-value
ALT	Pre-NAC	2306 ± 1533	1734 ± 1505	0.101
	24 hours post-NAC	n=40* 1129 ± 855	822 ± 730	
	ALT before discharge	389 ± 409	603 ± 613	
AST	Pre-NAC	2010 ± 1881	3579 ± 2027	<0.001
	24 hours post-NAC	n=16* 482 ± 493	629 ± 367	
	AST before discharge	434 ± 512	437 ± 198	
PT	Pre-NAC	36 ± 26	57 ± 43	0.01
	24 hours post-NAC	n=40* 19 ± 8	53 ± 41	
	AST before discharge	15 ± 4	52 ± 49	
INR	Pre-NAC	3.4 ± 2	4.5 ± 3	0.05
	24 hours post-NAC	n=40* 2.6 ± 3	4.5 ± 3	
	AST before discharge	1.8 ± 2	9.7 ± 15	
SBR	Pre-NAC	19.2 ± 17	14.8 ± 8	<0.001
	24 hours post-NAC	n=38* 17.2 ± 13	16.8 ± 11	
	AST before discharge	11.4 ± 9	20.2 ± 11	
Albumin	Pre-NAC	2.9 ± 0.5	2.6 ± 0.6	0.01
	24 hours post-NAC	n=37* 2.9 ± 0.5	2.9 ± 0.5	
	AST before discharge	2.8 ± 0.5	2.9 ± 0.6	

* Children with all laboratories available.
Abbreviations: ALT = Alanine transaminase; AST = Aspartate transaminase; PT = Prothrombin time; INR = International normalization ratio; SBR = Serum bilirubin.

14.3), need for mechanical ventilation at admission (OR 4.3; CI = 1.1 - 16.6) and inotropic support (OR 20.6; CI = 3.5 - 118.3) identified poor prognostic markers of mortality at univariate analysis.

DISCUSSION

Hepatitis A is endemic in many areas of the world including Pakistan where it has been reported to be the main cause (10 - 50%) of FHF death.^{6,18-20} Although the Hepatitis A co-infection with Hepatitis E virus has been associated with increased mortality,²¹ the authors found Hepatitis A FHF leading to mortality in more than half (55%) of the study cohort, as observed in other studies from the subcontinent.^{6,18} Medical literature about efficacy of NAC in childhood FHF because of AVH is very scarce and till date only two randomized clinical trials available compared the NAC efficacy in non-APAP FHF.^{12,13,22} One trial specifically in adult, with inconclusive results,¹³ while one trial performed in paediatrics,¹² with limited AVH FHF pathology showed some promising results particularly in centers without

Table IV: Mortality associated risk factor among children with AVH received N-acetylcysteine.

Variables	Survived (n=25)	Died (n=15)	p-value	OR (95% CI)
Male	17 (68%)	8 (53%)	0.50	0.53 (0.2 - 2.0)
Presenting complaints				
Fever	14 (56%)	6 (40%)	0.51	0.52 (0.1 - 1.9)
Abdominal pain / distension	9 (36%)	4 (26%)	0.73	0.55 (0.2 - 2.6)
Vomiting	20 (80%)	7 (46%)	0.03	0.22 (0.05 - 0.8)
Jaundice	15 (60%)	14 (93%)	0.03	9.3 (1.1 - 82.6)
Altered sensorium	11 (44%)	8 (53%)	0.56	1.5 (0.4 - 5.2)
Hematemesis*	1 (04%)	2 (13%)	0.54	
Complications				
Bleeding	0	3 (20%)	--	--
Grade-IV coma	0	10 (66%)	--	--
Acute kidney injury*	5 (20%)	7 (46%)	0.07	3.5 (0.9 - 14.3)
Hypoglycemia**	6 (24%)	6 (40%)	0.31	2.1 (0.5 - 8.4)
Electroencephalography				
Diffuse delta and theta slowing	10 (40%)	6 (40%)	0.32	1.6 (0.7 - 3.8)
Mechanical ventilation*	11 (44%)	13 (87%)	0.01	4.3 (1.1 - 16.6)
Renal replacement therapy*	4 (16%)	1 (06%)	0.63	--
Inotropic therapy	6 (24%)	13 (87%)	<0.001	20.6 (3.5 - 118.3)
Neuro-protective therapy	19 (76%)	12 (80%)	0.77	0.8 (0.2 - 3.8)

** Hypoglycemia (Random blood sugar <60 mg/dl); * Fischer Exact test applied

transplantation, where there is no other option for child survival.²³

Managing FHF is challenging because of its rapid progression to coma and death. It required early intervention and best possible supportive measures to correct and normalize metabolic parameters to reduce further hepatic injury.¹⁹ There was an overall steady improvement in LFTs over time after NAC administration. Despite the discharge disposition most of the LFTs in this study population showed improvement after NAC administration. However, the baseline laboratory parameters (i.e., PT and INR) were severely deranged in children in died group. These laboratory parameters if severely deranged at the time of admission has a worse prognosis.^{2,15,19} NAC benefits less in children with milder hepatic encephalopathy.¹² The authors observed marked changes and gradual improvement in LFTs over the time in children with milder hepatic encephalopathy compared to children developed coma. Almost all children with grade-IV hepatic encephalopathy died in the present cohort. Encephalopathy is one the main determinants of outcome.⁵ This study showed that 16 (40%) presented with altered level of consciousness while 11 (28%) had Glasgow Coma Scale (GCS) of less than 8; similar to previous studies and was also associated with higher mortality.^{5,18,21}

Most of the published medical literature proved NAC safety in children in paracetamol induced hepatic toxicity, and with growing literature its use in AVH induced FHF is safe and effective.^{24,25} There was an improvement in biochemical, metabolic and clinical parameters without any adverse effect (hypotension and anaphylaxis). The overall mortality in this study cohort was 38%, which is much less than previously described

at other centers without liver transplant in Pakistan and Turkey.^{1,18}

This study showed the same bad prognostic markers as already highlighted by many studies including encephalopathy on presentation, raised INR and bilirubin and a worsening trend of these parameters.^{1,4,22} Overall mortality due to FHF is decreasing with early liver transplant becoming available at some centers but it is still high (20 - 50%).^{1,18,22}

The limitation of this study includes retrospective data; we were not able to assess all the variables and were limited by the completeness of documentation by the treating physicians. It is also very difficult to ascertain the causality and whether improvements in clinical and laboratory parameters are due to spontaneous recovery over time or effect of NAC in the absence of control group. Because of the constraints of the chart review, not all confounding variables could be dealt with, but we performed a stringent statistical analysis i.e., repeated measures ANOVA design and adjusted odds ratio to reduce the impact of these variables to the lowest levels possible. There is no comparison group. The other possibilities for future is to either use historic control which itself has limitations or have a prospective control group. The authors identified certain important prognostic risk factors for AVH mortality along with safety and effectiveness of NAC in paediatric population over a period of time by checking the change in hepatic laboratory markers provides important knowledge in AVH and NAC in developing country setting where the hepatic transplantation facilities are essentially not available, however, an interventional blinded design with a comparative arm in paediatric population is important in this field.

CONCLUSION

NAC use in FHF secondary to AVH is effective in developing countries without liver transplantations facilities. It shows improvement in LFTs and encephalopathy. Further studies, including paediatric randomized trial on FHF secondary to AVH are needed before its routine use.

Acknowledgement: Dr. Ali Faisal Saleem received research training support from the National Institute of Health's Fogarty International Center (1 D43 TW007585-01).

REFERENCES

- Latif N, Mehmood K. Risk factors for fulminant hepatic failure and their relation with outcome in children. *J Pak Med Assoc* 2010;**60**:175-8.
- Lee WS, McKiernan P, Kelly DA. Etiology, outcome and prognostic indicators of childhood fulminant hepatic failure in the United Kingdom. *J Pediatr Gastroenterol Nutr* 2005; **40**: 575-81.
- O'Grady JG, Williams R. Classification of acute liver failure. *Lancet* 1993; **342**:743.
- Shah U, Habib Z. Liver failure attributable to hepatitis A virus infection in a developing country. *Pediatrics* 2000; **105**:436-8.
- Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, *et al.* Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr* 2006; **148**:652-8.
- Ciocca M, Moreira-Silva SF, Alegria S, Galoppo MC, Ruttiman R, Porta G, *et al.* Hepatitis A as an etiologic agent of acute liver failure in Latin America. *Pediatr Infect Dis J* 2007; **26**:711-5.
- Blackford MG, Felter T, Gothard MD, Reed MD. Assessment of the clinical use of intravenous and oral N-acetylcysteine in the treatment of acute acetaminophen poisoning in children: a retrospective review. *Clin Ther* 2011; **33**:1322-30.
- Zafarullah M, Li WQ, Sylvester J, Ahmad M. Molecular mechanisms of N-acetylcysteine actions. *Cell Mol Life Sci* 2003; **60**:6-20.
- Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, *et al.* Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology* 2009; **137**:856.
- Sotelo N, de los Angeles Durazo M, Gonzalez A, Dhanakotti N. Early treatment with N-acetylcysteine in children with acute liver failure secondary to hepatitis A. *Ann Hepatol* 2009; **8**: 353-8.
- Gunduz H, Karabay O, Tamer A, Ozaras R, Mert A, Tabak OF. N-acetylcysteine therapy in acute viral hepatitis. *World J Gastroenterol* 2003; **9**:2698-700.
- Squires RH, Dhawan A, Alonso E, Narkewicz MR, Shneider BL, Rodriguez-Baez N, *et al.* Intravenous N-acetylcysteine in pediatric patients with non-acetaminophen acute liver failure: a placebo-controlled clinical trial. *Hepatology* 2013; **57**: 1542-9.
- Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, *et al.* Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology* 2009; **137**:856-64, 64 e1.
- Lee WM, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. *Hepatology* 2008; **47**:1401-5.
- Bucuvalas J, Yazigi N, Squires RH Jr. Acute liver failure in children. *Clin Liver Dis* 2006; **10**:149-68, vii.
- Drug Information Handbook, 22th ed. Hudson, Ohio, *Lexi-Comp, Inc.*; 2013.
- Selvan VA, Calvert SH, Cavell G, Glucksman E, Kerins M, Gonzalez J. Weight-based N-acetylcysteine dosing chart to minimise the risk of calculation errors in prescribing and preparing N-acetylcysteine infusions for adults presenting with paracetamol overdose in the emergency department. *Emerg Med J* 2007; **24**:482-4.
- Aydogdu S, Ozgenc F, Yurtsever S, Akman SA, Tokat Y, Yagci RV. Our experience with fulminant hepatic failure in Turkish children: etiology and outcome. *J Trop Pediatr* 2003; **49**:367-70.
- Latif N, Mehmood K. Risk factors for fulminant hepatic failure and their relation with outcome in children. *J Pak Med Assoc* 2010; **60**:175-8.
- Shah U, Habib Z, Kleinman RE. Liver failure attributable to hepatitis A virus infection in a developing country. *Pediatrics* 2000; **105**:436-8.
- Arora NK, Nanda SK, Gulati S, Ansari IH, Chawla MK, Gupta SD, *et al.* Acute viral hepatitis types E, A, and B singly and in combination in acute liver failure in children in north India. *J Med Virol* 1996; **48**:215-21.
- Squires RH, Dhawan A, Alonso E, Narkewicz MR, Shneider BL, Rodriguez-Baez N, *et al.* Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: a placebo-controlled clinical trial. *Hepatology* 2013; **57**:1542-9.
- Sales I, Dzierba AL, Smithburger PL, Rowe D, Kane-Gill SL. Use of acetylcysteine for non-acetaminophen-induced acute liver failure. *Ann Hepatol* 2013; **12**:6-10.
- Kortsalioudaki C, Taylor RM, Cheeseman P, Bansal S, Mieli-Vergani G, Dhawan A. Safety and efficacy of N-acetylcysteine in children with non-acetaminophen-induced acute liver failure. *Liver Transpl* 2008; **14**:25-30.
- Parker D, White JP, Paton D, Routledge PA. Safety of late acetylcysteine treatment in paracetamol poisoning. *Hum Exp Toxicol* 1990; **9**:25-7.

