

N-acetylcystein in dengue associated severe hepatitis

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Abstract

Although, N-acetylcystein (NAC) has shown benefit in non-acetaminophen related liver failure, it was not well studied in dengue associated severe hepatitis. We report a case of dengue hemorrhagic fever associated severe hepatitis (encephalopathy grade 2-drowsy and intermittent disorientation) treated with NAC resulted in good outcome without hepatic transplantation.

Keywords: Dengue hepatitis, Dengue fever, N-acetylcystein, severe hepatitis

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.128712

Quick Response Code:



Introduction

Role of N-acetylcystein (NAC) in adults with non-acetaminophen induced liver failure was described in few studies in literature.^[1,2] Findings of Mumtaz *et al.* and Lee *et al.* studies were particularly relevant to countries where, liver transplantation facilities are limited or unavailable. Lee *et al.* found a significantly improved transplantation free survival at 3 weeks and at 1 year with the use of NAC in non-acetaminophen related liver failure, the benefit being confined to those with early hepatic encephalopathy.^[2]

Dengue infection is prevalent in Southeast Asia, and according to the Epidemiological Unit, Ministry of Health, Sri Lanka, during the last 4 months of the year 2012, 11148 suspected dengue cases and 46 deaths have been reported. The elevation of transaminases is usually less than five-fold greater than upper limit of normal. However, levels more than five-fold were reported 36.8% and 74.4% of patients with classical dengue and dengue

hemorrhagic fever (DHF) respectively. Fulminant hepatitis tends to occur more often in DHF or dengue shock syndrome compared to classic dengue infection and case fatality rate of 50% being reported.^[3] Although, NAC has shown benefit in non-acetaminophen related liver failure, it was not well studied in dengue associated severe hepatitis.

Case Report

A previously healthy 54-year-old mother of three admitted with 3 day history of fever, headache and body ache. Physical examination on admission was unremarkable. Investigation on the day of admission revealed Platelets 84,000/cumm and haematocrit (HCT) 37%. On the 2nd day, she was transferred to intensive care unit (ICU) as her platelets dropped to 41,000 per cu mm and HCT increased to 47%. Liver transaminases showed mild to moderate rise with ((AST) Aspartate transferase) 302 U/L and ((ALT) Alanine transferase) 262 U/L and patient was given total dose of 10 g of acetaminophen over 3 days at the time. She was resuscitated with ringer lactate according to the dengue protocol. She had stable hemodynamics apart from heart rate of 121 beats/min, but she developed right side moderate pleural effusion, icterus, mild ascites and right hypochondrial pain.

In the ICU, she deteriorated further, with a decline

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of Glasgow coma scale (GCS) to 11, but no focal neurological signs. Urgent computed tomography brain was done and it neither showed intracranial hemorrhage nor evidence of increased intracranial pressure. Her liver functions continued to deteriorate and liver enzymes reached peak value of AST 16261 U/L and ALT 4545 U/L, (PT/INR) prothrombin time/international normalized ratio 1.7 and total bilirubin 5.9 mg/dl on 4th day of admission (7th day of illness). Her renal function was never abnormal. Intravenous NAC was started at 100 mg/kg/day as an infusion and continued for 5 days with liver failure regime. Marked improvement in liver enzyme was noted and SGOT and SGPT levels dropped by more than half by 48 h of treatment. On the 9th day of admission, liver function revealed AST 300 U/L, ALT 223 U/L and PT/INR 1.2, and her conscious level improved to GCS of 15.

During the course of illness, she had mild gum bleeding and few ecchymotic patches with lowest platelet count of 18,000 per Cu mm. Her serology was positive for dengue antibodies but negative for hepatitis A and B. Hepatitis E serology was not done due to unavailability. Co-infection of malaria was not excluded as she was from neither endemic area nor her symptomatology typical of malaria including fever pattern. Possibility of leptospirosis cannot be excluded in this case as serology was not done. However, she did not have any exposure and her renal functions were never abnormal.

During her follow-up visit at 2 weeks after discharge, she had normal liver profile and did not have any evidence of chronic liver disease.

Discussion

Pathogenesis of liver involvement in dengue fever is complex and is poorly understood. Both virus itself and dysregulated immune response to virus are being described as possible mechanisms of liver damage in literature.^[3] Although, severe hepatitis associated with dengue fever is a rare occurrence, it carries significant mortality and morbidity.

NAC, mostly used in acetaminophen poisoning, acts through its antidote effect of repletion of hepatocellular glutathione stores. NAC scavenges free radicals, improves antioxidant defense and acts as a vasodilator to improve oxygen delivery and consumption.^[4] These

properties of NAC have been postulated to improve outcome in patient with dengue associated acute liver dysfunction. Lee *et al.* concluded that benefit is seen when NAC is used early stage of liver failure rather than late stage.^[2] A retrospective analysis on NAC in dengue associated liver failure by Kumarasena *et al.* showed that 5 patients who survived out of 8 were in early (coma grade 1, 11) liver failure stage at the time when NAC was started.^[5] This case report also supports the view that intravenous administration of NAC is safe and benefits patients, if started in early stage of liver failure.

This patient was treated with intravenous NAC 100 mg/kg/day infusion for 5 days compared to 150 mg/kg bolus over 15 min followed by 12.5 mg/kg/h for 4 h and then 6.25 mg/kg/h for 72 h was given by Kumarasena *et al.* in their retrospective analysis. Lim *et al.* reported a pediatric patient with dengue associated liver failure successfully treated with NAC and they have given intravenous NAC 100 mg/kg/day for 6 days. Thus, ideal regime of NAC in this situation needs to be determined.

Conclusion

This case report supports the use of NAC in dengue associated severe hepatitis. Large randomized trials should be carried out to establish its efficacy along with appropriate dosage, timing, and duration of treatment.

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How to cite this article: Habaragamuwa BP, Dissanayaka P. N-acetylcystein in dengue associated severe hepatitis. *Indian J Crit Care Med* 2014;18:181-2.

Source of Support: Nil, **Conflict of Interest:** None declared.