Editorial

The role of N-acetylcysteine in the treatment of non-acetaminophen acute liver failure

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Acute liver failure (ALF) is a rare critical illness, usually occurring in patients without underlying liver disease, which can cause significant mortality.[1] ALF has been known by many different terminologies including fulminant hepatic failure, hepatic necrosis, and fulminant hepatitis. While many definitions exist to characterize the process of ALF, the most widely used is the following: hepatic injury with the presence of encephalopathy and a coagulation abnormality usually manifested by an international normalized ratio (INR) of ≥1.5 typically in a patient without preexisting liver disease with an illness of <26 weeks' duration.[2] The incidence of ALF is estimated at 1–6 per 1 million population in the developed world, and is possibly even higher in the developing world where viral hepatitis is much more prevalent.[3] Survival from ALF has dramatically improved over the last several decades with the advent of liver transplantation and can exceed 65% in the developed world.[4] However, survival remains poor at 50% in some areas of the developing world where access to optimal medical care and liver transplantation may be limited.[5]

There are numerous causes of ALF, which include drugs, viral hepatitis, autoimmune hepatitis, vascular, metabolic disorders, and toxins.[1] There is a geographic variance in the distribution of causes with drugs, most notably acetaminophen, being the most common etiology in the Western world and viral hepatitis being the most common etiology in the Eastern World.[6] In a number of cases, the cause of ALF remains unknown despite an extensive work up. The hallmark of medical management revolves around supportive care in a monitored setting with appropriate improvement of hemodynamics, treatment of encephalopathy and cerebral edema, bleeding prevention when appropriate, correcting metabolic alterations, infection surveillance and treatment, nutritional support, and providing antidotes for the identified etiologies of ALF.[2,7] While a number of patients develop appropriate liver regeneration and recover with supportive care, in advanced ALF, liver transplantation is the only treatment option.[8] Several prognostic scores have been developed to identify these patients, and while most have inherent limitations, the Kings College Criteria remains the most widely used prognostic indicator for liver transplantation in ALF.[9]

N-acetylcysteine (NAC) is a glutathione precursor with antioxidant, anti-inflammatory, and vasodilator effects. NAC detoxifies the reactive metabolite of acetaminophen and restores hepatic glutathione levels.[10] Its effective role in acetaminophen-induced ALF is well established.[11,12] NAC has also been studied in non-acetaminophen ALF. A limited amount of prospective studies on this have been published, which have shown no improvement in overall survival, but improvement in transplant-free survival and post-transplant survival.[13] However, more work in this area is required.

In this edition of the journal, Nabi T, *et al.* further studied the utility of NAC in a non-acetaminophen ALF population with no access to liver transplantation.[14] This was a prospective study conducted in Southeast Asia consisting of 80 patients with non-acetaminophen ALF. Patients were equally randomized to an NAC infusion for 72 hours or placebo. There were no significant differences between the two groups in baseline characteristics except for age. The most prevalent underlying causes of ALF were undetermined, viral hepatitis, and drug induced or toxin. There was a statistically significant difference in mortality, which was 28% in the NAC group versus 53% in the placebo group ($P = 0.023$). Mannitol was used for raised intracranial pressure more frequently in controls (92.5%) than in the NAC group (75%) ($P = 0.037$). The mean number of days of admission to hospital for patients who survived was 8.2 in the NAC group versus 10.7 in the controls ($P = 0.002$). On logistic regression, not using NAC, stage 3–4 encephalopathy, and the presence of ascites were predictors of mortality. In conclusion, this study endorsed the use of NAC in non-acetaminophen ALF for patients at a non-transplant centre.

There are a number of inherent limitations of this study that should be mentioned. First, the authors determined if patients did not use acetaminophen based purely on clinical history and not a drug level of acetaminophen, which was not available at the institute. This could have possibly led

to the inclusion of some acetaminophen ALF patients in this study. In addition, the overall study size was quite small which could limit the statistical significance of the results obtained. There was also a statistically significant difference in the patient age between the two groups when looking at baseline characteristics. In the NAC group, the mean patient age was 30.6 years versus 38.5 years in the control group ($P = 0.035$). This could have possibly skewed the mortality benefit seen in the NAC group as younger patients are more likely to do better than older patients with a better reserve at baseline. In addition to the mortality difference seen between the two groups, it is interesting to note that patients receiving NAC were less likely to need mannitol for cerebral edema. This could possibly be related to the antioxidant, anti-inflammatory, and vasodilator effects of NAC.

In summary, when compared to the other prospective studies to date, this study shows a mortality benefit in overall mortality with NAC versus placebo. When all other available prospective studies were analyzed in a meta-analysis, a statistical significance in overall mortality was not seen except when looking at transplant-free survival or post-transplant survival.[13] This study examined the utility of NAC for non-acetaminophen ALF at a non-transplant center whereas transplant was available in the other studies. NAC should be considered in non-acetaminophen ALF, especially if transplant might not be an option, however, further studies are still required to solidify its use in this patient population.

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