N-Acetylcysteine in the Management of Acute Liver Failure From Sickle Cell Hepatic Crisis

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ABSTRACT
N-acetylcysteine (NAC) has been well studied in the treatment of acetaminophen-induced and select non-acetaminophen-induced liver failure. However, its role in the management of sickle cell hepatic crisis resulting in acute liver failure (ALF) is unknown. We describe and discuss the novel and beneficial use of NAC in a 25-year-old man with ALF due to sickle cell hepatic crisis. We further review ALF in sickle cell disease and NAC in the treatment of non-acetaminophen-induced liver failure. Our case highlights the promising role of NAC in sickle cell-related liver injury.

INTRODUCTION
Vaso-occlusive hepatic crises, which occur in roughly 10% of patients admitted with sickle cell disease (SCD) pain crisis, manifest with right upper quadrant abdominal pain, elevated levels of liver enzymes, and hyperbilirubinemia.1 Acute liver failure (ALF) is a rare but fatal complication of vaso-occlusive hepatic crisis. Early exchange transfusions are used as an attempt to reverse this process.2 N-acetylcysteine (NAC) in patients with SCD has shown promise in a randomized pilot study to reduce oxidative stress markers, central to the pathophysiology of sickle cell crises.3 However, NAC is not routinely used for hepatic manifestations of SCD. Our case report focuses on the presentation and management of ALF in a patient with SCD as well as the evaluation of NAC as a novel supplemental therapy.

CASE REPORT
A 25-year-old man with SCD and frequent pain crises presented with altered mental status and right upper quadrant pain. On presentation, his laboratory test results were notable for hyperbilirubinemia 60 mg/dL, from a baseline of 20 mg/dL, an unreportable aspartate aminotransferase (due to an overly icteric sample), alanine aminotransferase 74 U/L, alkaline phosphatase 57 U/L, and an initial international normalized ratio of 3.2. He had a hemoglobin level of 8.5 g/dL with a hemoglobin S fraction of 54.2%. The patient’s creatinine level was elevated at 3.4 mg/dL from the baseline 0.9 mg/dL. Serologic evaluation for alternate causes of liver disease including acute viral hepatitis was negative. Magnetic resonance imaging of the abdomen with contrast showed hemosiderosis of the liver (Figure 1). No liver lesions, biliary ductal dilation, or hepatic vascular obstruction was present.

Exchange transfusion was performed on hospital day 1, given the known benefit of early exchange transfusion in vaso-occlusive crises. Despite a successful reduction of hemoglobin S burden to 14.9%, the patient remained encephalopathic and coagulopathic (international normalized ratio 1.9–2.3). After the persistent lack of improvement by day 5, the decision was made to try intravenous NAC. The infusion was given as an initial loading dose of 150 mg/kg over the first hour, then 50 mg/kg over 4 hours, and finally as...
a continuous infusion of 100 mg/kg over the remaining 16 hours. The patient subsequently became more alert and interactive. The patient had repeat sickling with hemoglobin S fraction of 30% requiring a second exchange transfusion on hospital day 13. He became clinically stable and was discharged from the hospital on day 17 (Table 1).

**DISCUSSION**

ALF is a rare complication of vaso-occlusive crisis related to intrahepatic cholestasis in SCD and has been associated with a mortality of 40% in the absence of exchange transfusions. To date, management has been limited: exchange transfusion is a first-line treatment followed by supportive therapy. Exchange transfusion aims for rapid reduction of sickle cell fraction, ideally under 30%. This results in the reduction of viscosity associated with sickled cells and helps reverse the complications of acute anemia that would otherwise limit perfusion. Early exchange transfusion has been shown to reverse coagulopathy, reduce lactic acidosis, and improve hyperbilirubinemia in patients. In more isolated cases of SCD with ALF, transplant has been considered. Liver transplant in such patients is rare and risky, with over half of the patients suffering from complications including repeat vaso-occlusive crises, graft thrombosis, and infections.

NAC can be considered in non-acetaminophen-induced (NAI) ALF per 2011 American Association for the Study of Liver Diseases guidelines and is recommended for use in 2017 European Association of the Liver guidelines. NAC mitigates the detrimental effects of acetaminophen overdose through its ability to replete antioxidant glutathione stores and conjugate with N-acetyl-p-benzoquinone imine. Furthermore, the anti-inflammatory and antioxidant effects of NAC enhance oxygen delivery and perfusion.

### Table 1. Hospital course

| Hospital day | Intervention     | AST (U/L) | ALT (U/L) | Alkaline phosphatase (U/L) | Total bilirubin (mg/dL) | INR | PTT | Creatinine (mg/dL) |
|--------------|------------------|-----------|-----------|---------------------------|------------------------|-----|-----|-------------------|
| 1            | Exchange transfusion | 74        | 57        | 2                         | 2.3                    | 108.1 | 3.4 |
| 2            |                   | a         | a         | >60                       | 2.2                    | 109.7 | 3.7 |
| 3            |                   | a         | a         | >60                       | 1.9                    | 108.1 | 3.0 |
| 4            |                   | a         | a         | >60                       | 2.0                    | b    | 2.5 |
| 5            | NAC              | a         | 72        | 36                        | >60                    | 2.0   | 74.1 | 2.3 |
| 6            |                   | a         | 72        | 36                        | >60                    | 1.9   | b    | 2.0 |
| 7            |                   | a         | 66        | 36                        | >60                    | 1.9   | b    | 1.9 |
| 8            |                   | a         | 78        | 46                        | >60                    | 2.2   | b    | 1.7 |
| 9            |                   | a         | 46        | 31                        | 47.8                   | 2.3   | 132.1 | 1.7 |
| 10           |                   | a         | 78        | 46                        | >60                    | 2.0   | b    | 1.3 |
| 11           |                   | 122       | 75        | 53                        | 56.1                   | 2.2   | 101.7 | 1.7 |
| 12           |                   | 120       | 73        | 58                        | >60                    | 2.1   | 87.8 | 1.5 |
| 13           | Exchange transfusion | 118      | 67        | 57                        | >60                    | 2.0   | 64.5 | 1.2 |
| 14           |                   | 123       | 73        | 67                        | >60                    | 1.5   | b    | 1.2 |
| 15           |                   | 110       | 66        | 65                        | 56.7                   | 1.6   | 50.6 | 1.1 |
| 16           |                   | 89        | 65        | 68                        | 55.5                   | 1.7   | b    | 1.0 |
| 17           |                   | 91        | 64        | 70                        | 53.0                   | 1.6   | b    | 0.9 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; NAC, N-acetylcysteine; PTT, prothrombin time; RR, relative risk.

* Sample was too icteric for the value to be accurately reported.

b Not measured.
associated with mortality benefit and decreased hospital length of stay. In a prospective, double-blinded study of 172 patients with NAI ALF (81 NAC; 92 placebo), a 72-hour infusion of intravenous NAC significantly improved transplant-free survival at 3 weeks (40% vs 27%). Specifically, significant survival difference was noted in patients with hepatic coma scale I and II. However, the primary endpoint of overall survival was not significantly different between the groups.

This case report illustrates the novel use of NAC in sickle cell hepatic crisis. While this specific context (SCD hepatic crisis) is novel, the rationale behind the use of NAC in SCD is supported in several studies. Oxidative stress plays an important role in SCD and derives from unstable hemoglobin S, chronic intravascular hemolysis, and repeat cycles of ischemia reperfusion injury. Mutated hemoglobin S causes damage to red blood cell membranes via polymer formation and auto-oxidation, generating iron-mediated oxidants. Chronic, intermittent ischemia-reperfusion injury and resultant reactive oxygen species induce endothelial damage, accelerating hemolysis and inflammatory vasculopathy. Consequently, sickle cell patients often have depleted stores of intrinsic antioxidants, such as amino-thiol glutathione. As such, potential therapies have targeted the completed stores of intrinsic antioxidants, such as amino-thiol glutathione.18

NAC, which is the rate-limiting substrate for generating glutathione, increases the amount of glutathione available to scavenge reactive oxygen species, reducing oxidative stress and downstream complications. Furthermore, NAC has been shown to potentiate nitric oxide, an endogenous vasodilator that enhances perfusion, reducing the sequelae of a prolonged hypoxic environment. Despite promising results, existent SCD studies have limited patients and none evaluated the use of NAC in ALF related to SCD. Further studies are needed to better understand the use of NAC in sickle cell hepatic crises, such as in our patient. Given that management of SCD focuses conventionally on exchange transfusion, the clinical benefit of NAC in combination with exchange transfusion warrants investigation.

DISCLOSURES

Author contributions: X. Zhang interpreted the data and wrote and edited the manuscript. S. Burroughs, A. Farooq, and AJ Muir interpreted the data and edited the manuscript. YA Patel interpreted the data, reviewed the imaging, and edited the manuscript. JA Muir interpreted the data, reviewed the imaging, and edited the manuscript, and is the article guarantor.

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REFERENCES

1. Ebert EC, Nagar M, Hagopian KD. Gastrointestinal and hepatic complications of sickle cell disease. Clin Gastroenterol Hepatol. 2010;8(6):483–9; quiz e470.
2. Sheehy TW, Law DE, Wade BH. Exchange transfusion for sickle cell intrahepatic cholestasis. Arch Intern Med. 1980;140(10):1364–6.
3. Nur E, Brandjes DP, Tuerlink T, et al. N-acetylcysteine reduces oxidative stress in sickle cell patients. Ann Hematol 2012;91(7):1097–105.
4. Banerjee S, Owen C, Chopra S. Sickle cell hepatopathy. Hepatology. 2001; 33(5):1021–8.
5. Stephen JL, Merpit-Gonon E, Richard O, Raynaud-Ravni C, Freyon F. Fulminant liver failure in a 12-year-old girl with sickle cell anemia: Favourable outcome after exchange transfusions. Eur J Pediatr. 1995;154(6):469–71.
6. Shao SH, Orringer EP. Sickle cell intrahepatic cholestasis: Approach to a difficult problem. Am J Gastroenterol. 1995;90(11):2048–50.
7. O’Callaghan A, O’Brien SG, Ninkovic M, et al. Chronic intrahepatic cholestasis in sickle cell disease requiring exchange transfusion. Gut 1995;37(1):144–7.
8. Perini GF, Santos FP, Ferraz Neto JB, Pasqualini D, Hamerschlag N. Acute sickle hepatic crisis after liver transplantation in a patient with sickle beta-thalassemia. Transplantation. 2010;90(4):463–4.
9. Meekeel KL, Langham MR, Jr, Gonzalez-Peralta R, Fujita S, Hemming AW. Liver transplantation in children with sickle-cell disease. Liver Transpl. 2007;13(4):505–8.
10. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases position paper on acute liver failure 2011. Hepatology. 2012;55(3):965–7.
11. Wendon J, Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047–81.
12. Heard KJ. Acetylcysteine for acetaminophen poisoning. N Engl J Med. 2008;359(3):285–92.
13. Harrison P, Wendon J, Williams R. Evidence of increased guanylate cyclase activation by acetylcysteine in fulminant hepatic failure. Hepatology. 1996; 23(5):1067–72.
14. Nabi T, Nabi S, Rafiq N, Shah A. Role of N-acetylcysteine treatment in non-acetaminophen-induced acute liver failure: A prospective study. Saudi J Gastroenterol. 2017;23(3):169–75.
15. Lee WM, Hynan LS, Rossaro L, et al. Intraheprenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology. 2009;137(3):856–64, 864 e851.
16. Manwani D, Frenette PS. Vaso-occlusion in sickle cell disease. Pathophysiology and novel targeted therapies. Blood. 2013;122(24):3892–8.
17. Browne P, Shalev O, Hebbel RP. The molecular pathobiology of cell membrane iron: The sickle red cell as a model. Free Radic Biol Med. 1998;24(6):1040–8.
18. Ren H, Ghebremeskel K, Okpala I, Lee A, Ibegbulam O, Crawford M. Patients with sickle cell disease have reduced blood antioxidant protection. Int J Vitam Nutr Res. 2008;78(3):139–47.
19. Pace BS, Shartava A, Pack-Mabien A, Mulekar M, Ardia A, Goodman SR. Effects of N-acetylcysteine on dense cell formation in sickle cell disease. Am J Hematol. 2003;73(1):26–32.

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