Case report
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Two adolescent cases of early use of Molecular Adsorbent Recirculating System® for drug-induced fulminant hepatic failure

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Abstract

Fulminant hepatic failure (FHF) is a rare but fatal disease with a 40%-80% mortality, often requiring liver transplantation, which is hard to perform in children. A therapeutic intervention alternative to liver transplantation is an extracorporeal artificial liver support system. Molecular Adsorbent Recirculation Systems® (MARS) has emerged as a bridge therapy for adult FHF, whereas in pediatric FHF, there have been a small number of cases of implementing MARS. Recently, we witnessed the recovery of 2 teenagers with FHFs caused by acetaminophen and a diet aid. Both patients were treated uneventfully, with early use of MARS. These cases suggest that early use of MARS may be a promising therapeutic intervention in pediatric drug-induced FHF.

Key words: Drug-Related Side Effects and Adverse Reactions; Liver, Artificial; Liver Failure, Acute; Liver Transplantation; Pediatrics

Introduction

Fulminant hepatic failure (FHF) in children is a rare but fatal complication of acute liver diseases, and typically needs liver transplantation (LT) (1,2). However, when LT is definitely indicated, it is frequently postponed due to the lack of donors or the poor health of recipients. Even if LT is successfully performed, they may also be at risk of postoperative complications and lifelong immunosuppressive therapy (3). An alternative to LT may be an extracorporeal artificial liver support system, such as Molecular Adsorbent Recirculation Systems® (MARS) (4). Based on the principle of albumin dialysis, MARS removes protein-bound toxins accumulated in liver failure (5). Theoretically, it can remove albumin-binding substances (e.g., urea, creatine, bilirubin, bile acids, amino acids, and nitric oxide) and water-soluble substances (e.g., ammonia, and various types of drugs and toxins) (5).

Although MARS may be effective as an alternative to LT or a bridging role in adult FHF, few relevant pediatric cases have been reported without a randomized controlled trial (4,6). We present 2 adolescents with drug-induced FHF who successfully recovered without requiring LT through early application of MARS.

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Case

1. Case 1

This patient was a 15-year-old boy who had been diagnosed with fibromyalgia and an anxiety disorder.

He was found unconscious and presumed to have consumed a large amount of benzodiazepine when visiting the emergency department. The initial vital signs were as follows: blood pressure, 101/57 mmHg; heart rate, 85 beats/minute; respiratory rate, 22 breaths/minute; temperature, 36.4 ℃; and a Glasgow Coma Scale (GCS) score of 9. The initial chest plain radiograph and computed tomography showed nodular and patchy consolidations in dependent portions of both lungs without a pathogen isolated. Consequently, he was diagnosed with aspiration pneumonia and benzodiazepine intoxication. On the same day, the vital signs soon deteriorated as follows: blood pressure, 59/36 mmHg; heart rate, 81 beats/minute; respiratory rate, 11 breaths/minute; and temperature, 36.0 ℃. He underwent mechanical ventilation in the intensive care unit. On day 2, laboratory findings were as follows: total bilirubin (TB), 3.79 mg/dL; creatinine (Cr), 1.15 mg/dL; prothrombin time international normalized ratio (INR), 1.88; aspartate aminotransferase (AST), 183 U/L; and alanine aminotransferase (ALT), 164 U/L. On day 3, he was found to have consumed acetaminophen (AAP), not benzodiazepine.

The estimated dose of ingested AAP was higher than 300 mg/kg. Although 50 hours had already elapsed, we immediately started intravenous infusion of N-acetylcysteine as per the 21-hour protocol. On day 4, his laboratory findings deteriorated rapidly as follows: TB, 1.76 mg/dL; Cr, 0.65 mg/dL; INR, 4.02; and AST and ALT, both higher than 5000 U/L. Ultrasonography showed hepatomegaly and cholecystic edema with a moderate amount of ascites, which was considered a secondary change due to diffuse liver disease. A follow-up GCS score was 4 despite the limited assessment of mental status owing to sedation. A blood gas analysis showed a pH of 7.2. According to the "King's College criteria," the acidosis, as well as the increases in values of INR, AST, and ALT, indicated FHF and need for LT (2,7).

Despite the urgent need for LT, prompt surgery was infeasible due to uncontrolled infection and hemodynamic instability. In spite of antibiotic therapy, he was suffering from consistently high fever and C-reactive protein concentration (up to 11.6 mg/dL) due to aggravation of the aspiration pneumonia, and was administered a vasopressor to correct hypotension (down to 59/36 mmHg). Considering this ongoing instability, we had to find an alternative to LT. Thus, we started MARS on day 4. During the 8-hour session of MARS, dopamine and furosemide were continuously infused against hypotension and anuria, respectively. Intermittent desaturation down to 79% prompted a rise in FiO_2 to 100% in the ventilator setting.

Although the desaturation rendered the application of MARS difficult, hemostatic instability did not occur at a pre-application level. Thereafter, he showed an improvement in laboratory findings (Fig. 1A). The patient's mental status became alert with a GCS score of 14-15. On day 5, MARS was finished, pneumonia had resolved, and he was extubated. On day 8, he was transferred to the ward. On day 14, he was discharged without any complications.

2. Case 2

This patient was a 17-year-old girl who had consumed a diet aid containing catechin, vitamin C, and vitamin D for 2 weeks. During the period, she had lost 10 kg of weight. After 2 weeks, she started to feel worsening abdominal pain and visited a doctor. Given a presumptive diagnosis of FHF based on high concentrations of AST and ALT, the doctor transferred her to our hospital for a possible need for LT. The initial vital signs were as follows: blood pressure, 102/68 mmHg; heart rate, 62 beats/minute; respiratory rate, 20 breaths/minute; and temperature, 36.4 ℃. The initial laboratory findings were as follows: TB, 4.44 mg/dL; Cr, 0.6 mg/dL; INR, 3.57; AST, 1,822 U/L; and ALT, 4,039 U/L, supporting the FHF as her diagnosis. However, she was not classified as a candidate for emergency LT because her end-stage liver disease score was 28, which was relatively low enough to be considered a candidate for the surgery. Her family members were not matched with her as living donors. Hence, she was transferred to the intensive care unit and underwent 1

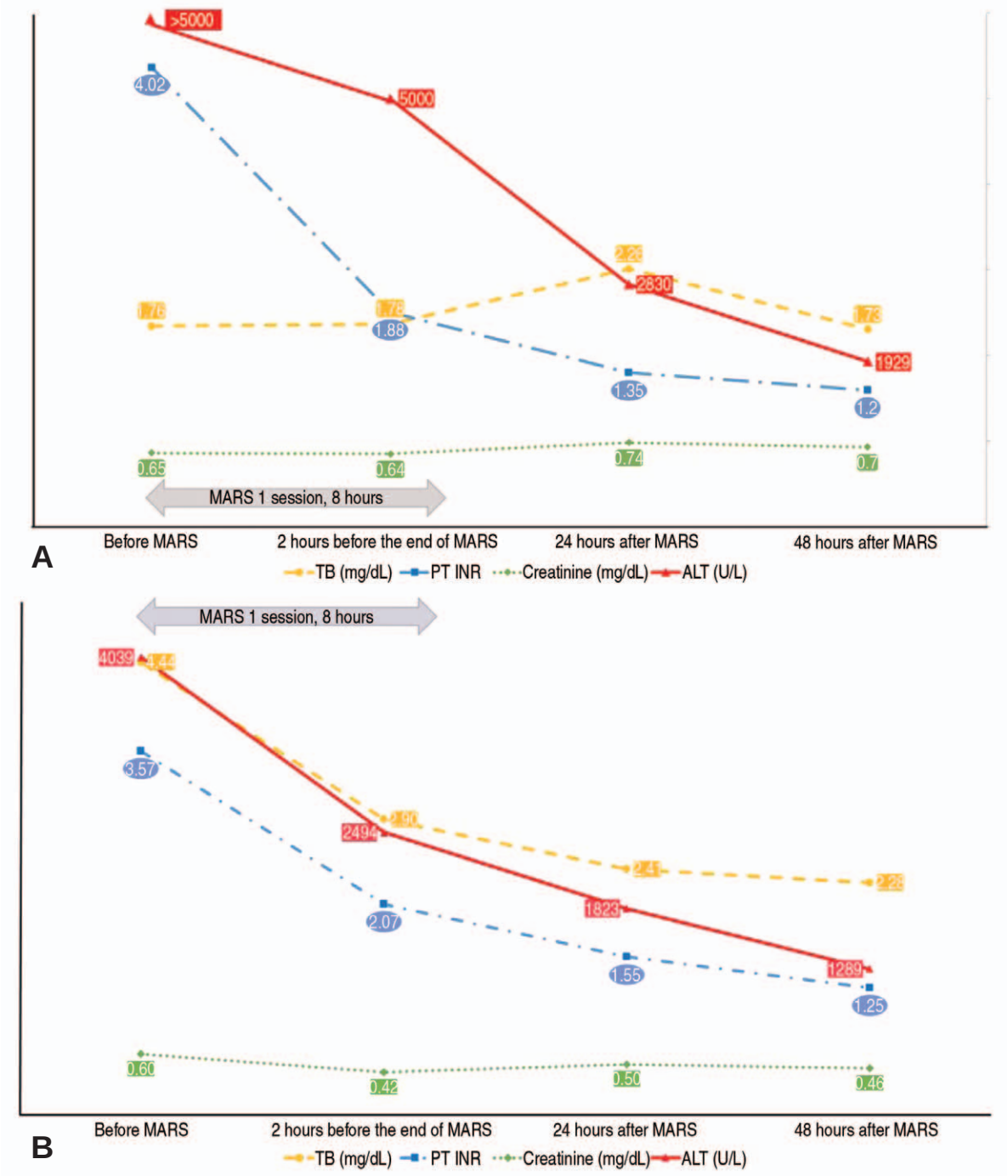

Fig. 1. Improvements in hepatic parameters before and after the sessions of MARS®. The parameters are listed in the order of TB, creatinine, PT INR, aspartate aminotransferase (not shown in the figures), and ALT. (**A**) A 14-year-old boy with acetaminophen-induced fulminant hepatic failure showed the following serial values. Two hours before termination of the session: 1.78 mg/dL, 0.64 mg/dL, 1.88, 2,685 U/L, and higher than 5,000 U/L; 24 hours after the session: 2.26 mg/dL, 0.74 mg/dL, 1.35, 854 U/L, and 2,830 U/L; and 48 hours after the session: 1.73 mg/dL, 0.70 mg/dL, 1.20, 230 U/L, and 1,929 U/L. (**B**) A 17-year-old girl with fulminant hepatic failure due to a diet aid showed the following serial values. Two hours before termination of the session: 2.9 mg/dL, 0.42 mg/dL, 2.07, 772 U/L, and 2,494 U/L; 24 hours after the session: 2.9 mg/dL, 0.42 mg/dL, 2.07, 772 U/L, and 2,494 U/L; and 48 hours after the session: 2.28 mg/dL, 0.46 mg/dL, 1.25, 203 U/L, and 1,289 U/L. MARS: Molecular Adsorbent Recirculating System, TB: total bilirubin, PT INR: prothrombin time international normalized ratio, ALT: alanine aminotransferase.

session of MARS on day 1. During the session, vital signs were maintained stable. Afterward, her laboratory findings improved (Fig. 1B). She was transferred to the ward on day 4 and was discharged uneventfully on day 12.

Discussion

The utility of MARS in patients with FHF is still being debated, and its indications are not established well (4). Although the use of MARS in adults has shown improvement in neurological status, no mortality benefit has been demonstrated by either meta-analyses or randomized clinical trials (4). However, since LT is sometimes infeasible in pediatric FHF, MARS could serve as a bridge to or replace LT (8). Although MARS can be applied to FHF of various etiologies, drug-induced FHF may be the optimal indication as in our case (8). This is because, unlike viral hepatitis, the main mechanism of drug-induced FHF is the rapid accumulation of toxins, which causes hepatic coma, rather than damage to the liver parenchyma (8). MARS is known to be effective in reducing plasma drug concentrations (9).

Two adolescents with FHF, one caused by AAP and the other by a diet aid, underwent early implementation of MARS. Each patient successfully completed a single session without notable complications. Afterward, we confirmed rapid decreases in INR and ALT, representative markers of treatment for FHF. In addition, the neurological status and general condition improved rapidly (2,4). In children, if a session of MARS is short, a decrease in serum bilirubin may be insufficient. To deal with such a situation, the session can be lengthened (4).

The most serious complications of MARS are coagulopathy and bleeding, which were not observed in our cases (4,6,8). Patient 1 with hypotension and oliguria was treated with conservative treatment with dopamine and furosemide, and successfully recovered through the application of MARS. According to the cases reported from other institutions, hemodynamic instability more often occurred in infants than adolescents. We have not yet applied MARS to young children or infants with FHF.

After the implementation of MARS, patient 1 has often visited our pediatric outpatient department for his underlying disease, and has been doing well for 2 years without complications of FHF. Patient 2 has also visited our hospital, and has been healthy till now. Their long-term outcomes have not yet been known because of the short follow-up periods. In conclusion, it is necessary to consider the early application of MARS to pediatric patients with drug-induced FHF.

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