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Case report

First case report of high volume therapeutic plasma exchange as a rescue therapy in dengue hemorrhagic fever with acute liver failure

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Acute liver failure is a rare but life-threatening complication of severe dengue infection. Besides standard medical treatment, high volume therapeutic plasma exchange (HV-TPE) is a potential management strategy used to reverse hepatic encephalopathy and coagulopathy. HV-TPE, moreover, improves patient survival from acute liver failure due to paracetamol overdose, viral-induced hepatitis, and Wilson disease. The use of HV-TPE in acute liver failure with dengue hemorrhagic fever has never been reported. We, hereby, report a successful treatment with HV-TPE in acute liver failure with dengue hemorrhagic fever.

Keywords: Case report, high volume therapeutic plasma exchange, acute liver failure, dengue.

Dengue infection is endemic in Southeast Asia. The incidence of hepatic involvement is up to 80.0% of patients and is usually mild.[1,2] Many factors may contribute to liver dysfunction, including hypoxic injury due to hypoperfusion, direct damage by the virus, and immune-mediated injury. Acute liver failure can rarely occur and is associated with poor outcomes with a 50.0 - 80.0% mortality rate.[3] This condition can result in life-threatening cerebral edema, hepatorenal failure and can rapidly progress to coma and death. Besides standard medical treatment, high volume therapeutic plasma exchange (HV-TPE) is a potential management strategy that is used to reverse hepatic encephalopathy, coagulopathy and improve survival in patients with acute liver failure from paracetamol overdose, viral-induced hepatitis, and Wilson disease.[4 - 6] However, the use of HV-TPE in dengue hemorrhagic fever with acute liver failure has never been reported.

HV-TPE can remove toxic factors such as circulating filaments, proteins, or vasoactive substances.[7] This treatment, therefore, may have a potential role in managing acute liver injury by dengue infection. We report that the successful treatment of acute liver failure in dengue hemorrhagic fever with HV-TPE serves as rescue therapy.

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Case report

A 27-year-old woman was admitted to a private hospital with a 5-day history of fever with chill and arthralgia. She had no history of alcohol and drug use. She had no significant medical history. On examination, her temperature was 37.8 c, her heart rate was 110/min and blood pressure was 100/60 mmHg. Examination demonstrated icteric sclera, right upper quadrant abdominal tenderness, hepatomegaly, and multiple petechiae at both extremities. Her Glasgow Coma Scale was 15 of 15.

Investigation revealed hemoconcentration (Hb 14.2 g/dL), severe thrombocytopenia (Platelet 15,000/ mm^3), elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic acidosis (Table 1). Chest x-ray showed small right pleural effusion. Diagnosis of dengue infection was confirmed by dengue polymerase chain reaction (PCR) positive for type 1. Other causes of illness were excluded by a negative test for hemoculture for bacteria, Chikungunya PCR, malarial antigen, leptospiral antibody, and rickettsial antibody. Her hepatitis profile, such as HBs Ag and anti-HCV antibody, was uneventful.

During hospitalization, her liver function continued to deteriorate (Table 1). Lactic acidosis occurred, and hemoglobin also dropped from baseline

without an obvious source of bleeding. Multiple red blood cell transfusion was required to maintain a hemoglobin level of above 15 g/dL. Fluid resuscitation and bicarbonate therapy were used to maintain hemodynamic according to local guidelines (pulse pressure greater than 20 mmHg, blood pH higher than 7.35, and urine output more than 0.5 ml/kg/hr). On the 3rd day of hospital admission, she was transferred to the intensive care unit in Prapokklao Hospital because of worsening oxygenation, altered mental status, and worsening liver function. She was intubated for airway protection because of grade III hepatic encephalopathy and received assisted ventilation due to metabolic acidosis. Sedation with propofol, fentanyl and midazolam were used to control ventilation and decrease oxygen consumption. Norepinephrine was used 0.3 - 0.5 ug/kg/min for maintaining mean arterial pressure above 65 mmHg. Intravenous N-acetylcysteine (NAC) was started at 150 mg/kg/day. The infusion continued over 24 hrs. This dosing was administered for 4 days until AST was less than 1,000 U/L. Worsening of liver function, lactic acid level, and creatinine are summarized in Table 1.

This deterioration prompted the use of high volume therapeutic plasma exchange (HV-TPE), which was done by the Haemonetics Multicomponents System (MCS) plus apheresis system based on intermittent flow centrifugation. It exchanged 8 liters with fresh frozen plasma for 8 hours per session for 3 consecutive days. Renal replacement therapy was started as well because of acute renal failure.

The patient showed improvement in lactate clearance and hemodynamic. By the end of the 3rd session, lactic acid returned to near normal, and vasopressor was discontinued.

Liver enzymes, total bilirubin, coagulopathy progress were normalized. The patient was subsequently extubated in the next 7 days and discharged from Intensive Care Unit (ICU) on day 23 after admission. The patient was successfully discharged from hospital day 28. Two weeks later, the patient was followed up. Her renal function and liver function returned to normal.

Discussion

Dengue infection is associated with a broad spectrum of illness severity ranging from dengue fever to dengue shock syndrome with multiple-organ failure.[8] From a liver perspective, liver involvement in dengue infection is common.[9] Mild transaminitis (transaminase of fewer than 5 folds increased) is observed in most patients.[10] Significant elevation of transaminase by more than 10 folds is rare, and acute liver failure rarely develops.[11-12] One study in Thailand estimated a 0.3% incidence of acute liver failure secondary to dengue infection.[13] The management of patients with acute liver failure is supportive care that includes supportive therapy for hypoglycemia, coagulopathy, encephalopathy, and cerebral edema.[14] Newer medical treatments include NAC, plasma exchange, and an extracorporeal system like the Molecular Adsorbent Recirculating System (MARS).[2, 14–15] Liver transplantation is undertaken

Table 1. Biochemical profile throughout the course of hospitalization.

	Hospital admission	ICU admission	Before HV-TPE	After 1st session of HV-TPE	After 2nd session of HV-TPE	After 3rd session of HV-TPE	ICU discharge
Hospital day	1	3	4	5	6	7	23
ALT	414	1520	3920	2048	52	109	119
AST	988	5290	19321	12113	190	351	123
TB	5.1	7.3	8.0	9.2	6.5	12.5	9.3
INR	2.2	2.2	2.7	1.7	1.2	1.4	1.2
MELD score	24	36	39	34	29	33	19
Lactate (mmol/L)	10.9	18.1	21.6	17.5	7.5	4.4	1.2
Hemoglobin (g/dL)	14.2	12.1	11.6	14.3	11.3	11.6	9.7
Platelets	15,000	18,000	23,000	27,000	27,000	38,000	120,000

HV-TPE = high volume therapeutic plasma exchange; ALT = alanine transaminase (U/L); AST = aspartate transaminase (U/L); TB = total bilirubin (mg/dL); INR = international normalized ratio; MELD score = Model for End-Stage Liver Disease.

once the liver has failed. MARS and liver transplantation are not available in our institution, and a referral to another center was not considered due to hemodynamic instability, severe coagulopathy, and organ dysfunction.

Our patient had acute liver failure with acute renal failure, lactic acidosis, and hepatic encephalopathy, requiring intubation and assisted ventilation. The relentless progression of the liver failure, prompted the use of intravenous NAC and HV-TPE which is novel in this setting.

High volume therapeutic plasma exchange (HV-TPE) is defined as the exchange of 8 -12 liter or 15.0% of ideal body weight with fresh frozen plasma.[5] This technique has a beneficial effect on delivering physiologically important substance contents in fresh frozen plasma and removing toxic factors, such as circulating filaments, proteins, or vasoactive substances.[7]

A systematic review of TPE for acute liver failure shows improvement in the survival of a patient who did not undergo a liver transplant.[6] The level of evidence for use of HV- TPE in selected acute liver failure cases is high. A randomized control trial on the use of HV-TPE in a patient with acute liver failure indicated improvements in liver transplant-free survival when compared with standard medical treatment.[5] Although the current guidelines, established in 2019 by the American Society for Apheresis (ASFA), give a strong recommendation grade 1A for using HV-TPE in acute liver failure[15], its use in dengue-related liver failure has not been reported. A previous report used low volume therapeutic plasma exchange (LV-TPE) as a therapeutic option for the treatment of acute liver failure (ALF) in dengue infection with unsatisfactory outcomes.[16 – 17] Only 2 of 4 patients with dengue-induced acute liver failure survived after undergoing LV-TPE. These patients were hemodynamically stable without vasopressor support before initiation of LV- TPE.

On the contrary, the other 2 hemodynamically unstable patients who required vasopressor support before initiating LV-TPE did not survive at the end of treatment. HV-TPE can remove the toxic factors mentioned above.[7] This treatment can decrease the severity of hepatic encephalopathy and vasopressor requirements[18]; therefore, it may have a potential role in managing acute liver injury caused by dengue infection.

The clinical and laboratory criteria for timing and mode of HV-TPE initiation are still evolving and far from complete. Our patient was initiated HV-TPE within 24 hours after developing grade III hepatic encephalopathy. This practice was comparable with previous studies in that HV-TPE was initiated within 24 hours of the development of grade II-III hepatic encephalopathy. Our study also adopted a strict consecutive daily 3-d therapeutic plasma exchange regimen in the open randomized control trial by Larsen FS.[5] However, some case reports operated differently by continuing the plasma exchange until their patients died, improved clinically, or received liver transplants at an average of 1 day to 36 days. For example, the case series of Buckner et al. showed that their patient with ALF from halothane toxicity received HV-TPE daily for 36 days until she recovered from a coma.[19]

Our patient responded to HV-TPE with the improving her liver function and coagulation plus the decrease in the MELD score. This case report suggests that HV-TPE can help support liver function and increase the time for hepatocyte regeneration. Our finding was comparable to studies done by Freeman JG, *et al*.[20] and Larsen FS, *et al*.[5] in the aspect that the survival group was related to liver function recovery and MELD score improvement after HV-TPE.

The fluctuating level of bilirubin may occur after treatment due to the ongoing inflammatory process of dengue infection, which can reduce the diameter of the lumen of the biliary canaliculus.[21]

Other mechanisms such as a delayed excretion of bilirubin due to acute renal failure, sepsis-induced cholestasis, and drug-induced cholestasis should also be considered as a cause of this finding.

HV-TPE's potential complications are anaphylaxis, fluid overload, lung injury, metabolic derangement, such as hypocalcemia and metabolic alkalosis.[15] This study used HV-TPE, whose complications rarely developed.[6] No serious adverse event was observed in our patient during the HV-TPE. The only significant observation was hypocalcemia and metabolic alkalosis. It was detected and corrected without other complications. Hypocalcemia was detected by monitoring serum calcium during this procedure and corrected by slow infusion of 10.0% calcium gluconate when serum calcium was less than 7.5 mg/dL. Metabolic alkalosis was detected by monitoring arterial blood gas and corrected by adjusting mechanical ventilator to decrease the minute ventilation.

Conclusion

To our knowledge, this is the first case report of successful treatment with HV-TPE in acute liver failure cause by dengue hemorrhagic fever. We propose that HV-TPE is safe and effective in dengue-associated acute liver failure, especially in a situation when MARS and liver transplantation are not available.

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