

Hemoadsorption Therapy for Expanded Dengue Syndrome Patients : A Case Series Study

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Abstract

Background: Dengue is a tropical infection transmitted by mosquitoes. It manifests expanded spectrum of diseases from mild to severe form. Pathogenesis of dengue causes thrombocytopenia by immune destruction which may cause bleeding manifestation and also a high viral load causes activation of T cell that make "storm" of inflammatory cytokines, leading to huge plasma leakage as a result patient develop haemo-concentration and shock. Expanded dengue syndrome is a rare category of dengue infection that involves multiple organs of the body and bears a fatal outcome.

Hemoadsorption is an extra-corporeal blood purification method used to reduce excess inflammatory mediators from blood. It is a haemo-adsorption procedure that was approved as an adjunct therapy for the management of sepsis and other high inflammatory conditions.

Case Presentation: We present three (3) cases of Expanded Dengue Syndrome along with fatal complications that were managed by hemoadsorption therapy. All the patients were treated in the intensive care unit (As per national guideline of Dengue) with fluids, antibiotics, oxygen supplement, non-invasive ventilation etc. when patient's condition did not improved after using all of these interventions, hemoadsorption therapy was introduced. After application of hemoadsorption therapy, all the patients were fully recovered without any residual disability. They were discharged on the 12th, 10th and 8th days of hospital stay respectively. when there is evidence of multi organ involvement in dengue fever, the disease burden is increased and treatment with such manifestations gets very challenging.

Conclusion: Hemoadsorption therapy can be an effective adjunct therapy for expanded dengue syndrome patients.

Key words: Acute Respiratory Distress Syndrome (ARDS); Cytosorb; Dengue shock syndrome (DSS); Expanded Dengue Syndrome (EDS); Hemoadsorption.

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Introduction

Dengue fever is a mosquito-borne tropical disease caused by dengue virus. *Aedes aegypti* mosquitoes and, to a lesser extent, *Aedes albopictus* transmit dengue viral infection to human. 'Dengue virus (DENV) has four serotypes (DENV-1, DENV-2, DENV-3, DENV-4). sequential infections with a different serotype put people at greater risk for severe dengue. Many DENV infections produce only mild flu-like illness and over 80% of cases are asymptomatic'.¹ In 2009 the World Health Organization (WHO) classified dengue into 2 major categories: dengue (With/without warning signs) and severe dengue.² Afterwards, in 2011, they coined the term Expanded Dengue Syndrome (EDS) in their guidelines to describe the atypical manifestations which were uncommon but increasingly recognized mostly in Southeast regions.¹ Most of the dengue patients recover within a week or so. In about 5% of cases, symptoms worsen and can become life-threatening.³ These atypical and unusual organopathies include intricacies of major organs, such as the liver, kidney, heart, lungs and nervous system and could be explained as complications of severe profound shock or associated with underlying host conditions or co-infections. Existing evidence indicates that EDS is associated with high mortality, morbidity, prolonged hospital stays and healthcare expenditure.⁴

In line with WHO, Bangladesh also updated their national guidelines in 2018 to include this syndrome in disease classification.² As of 31 December 2023, the Directorate General of Health Services (DGHS) has reported 321,179 hospitalizations and 1,705 deaths due to the *Aedes* mosquito-borne tropical disease in the 2023 outbreak year.⁵ But the data is sparse about EDS cases. There was a rising trend in the EDS cases throughout Dhaka city and only few were reported.⁶⁻⁷ EDS cases could be a potential contributor to death therefore, high index of suspicion and prompt targeted investigations are imperative for early detection of these cases.

As of 31 December 2023, the Directorate General of Health Services (DGHS) has reported 321,179 hospitalizations and 1,705 deaths due to the Aedes mosquito-borne tropical disease in the 2023 outbreak year.⁸

The hallmarks of DSS (Dengue Shock Syndrome) are endothelial cell activation and glycocalyx degradation leading plasma leakage through disrupted endothelial barrier. In addition, reduced nitric oxide bio availability causes impaired microvascular tone.⁹ Some pathological conditions, trigger a deregulated high immune response and cause massive elevation of cytokine levels (Cytokine storm) which ultimately lead to multi organ dysfunction. Despite the use of advance resuscitative strategies like the use of broad spectrum antibiotics, steroids, vasopressors inotropes and even mechanical ventilation, these cannot decrease the high mortality rate. In case of multi organ dysfunction, hemoabsorption therapy can be added as an adjunct therapy to eliminate excess inflammatory cytokines from blood. The effectiveness of various blood purification methods, 'including high-cut-off membranes, high-volume hemofiltration, adsorption techniques and albumin dialysis for removing cytokines and endotoxin and improving hemodynamic stability'.¹⁰

These patients were observed in a private hospital at the time of outbreak of dengue that occurred in Bangladesh from April to September 2023 in port city chittagong. These patients were treated in intensive care unit in a private hospital. When protocolized management failed to yield an adequate response, hemoabsorption using the cytosorb device initiated. Cytosorb is a special type of dialyzer that attached to conventional dialysis machine which is connected with blood line by a vascular access like fistula, graft or dialysis catheter. The content of the Cytosorb cartridge consists of a highly porous, high-tech polymer that provides a total surface area of > 45,000 square meters (>4 large football fields) and can adsorb effectively (Over 24 hours' time) up to a size of approximately 60kDa. The tiny beads can bind to a wide range of inflammatory mediators, such as e.g. cytokines, chemokines, and anaphylline toxins, myoglobin, bilirubin and bile acids, bioactive lipids, antibody light chains, etc. The removal of these substances is concentration-dependent, which helps to prevent complete removal of physiologic mediators.¹¹

Case I

Mr Z.H. a 25-year-old male, was admitted into a private hospital of Chattogram on 10th August, 2023 presented with fever for 5 days and with severe body ache, vomiting and severe abdominal pain. During admission his BP was normal, mildly dehydrated and patient was awake and alert. Investigations showed Dengue NS1Antigen and ICT for Dengue IgM positive with low platelet. (Platelet count $15 \times 10^9/L$) Neutropenia (WBC count $3.75 \times 10^9/L$) and was increased (47.6%).

He was categorized as a case of severe dengue with warning signs and treated accordingly. But after 48 hours, patient became disoriented and restlessness and was found icteric. He was diagnosed as hepatic encephalopathy which was supported by S. bilirubin - 2.80 mg/dl, SGOT - 2248 U/L, SGPT - 3194 U/L, S. albumin - 2.7 gm/dl, Prothrombin time (Control -13.4 s, patient -32.29s) with INR: - 2.41. Then patient was transferred to ICU and levelled as expanded dengue syndrome. Investigation also showed Troponin I - 8400 ng/ml (Ref value: <47 ng/ml), NT Pro-BNP-841 pg/ml, S. creatinine 1.5 mg/dl and Chest x-ray revealed extensive bilateral opacities. His IL -6 level was 79 (Ref value < 7 pg/ml) that was increased and procalcitonin was 3.5.ng/ml (Reference value less <0.1ng/ml). His oxygen demand was increasing. So, high flow oxygen through CPAP was given.

Despite the above measures, patient's condition was rapidly deteriorating (GCS 4/15) and patient became hemodynamically unstable. So it was decided to give him hemoabsorption therapy on the 9th day of his illness. After giving hemoabsorption therapy, patient was improving clinically with decreasing oxygen requirement and radiological improvement of chest X-ray and all lab parameters return to normal. On 12th day of admission patient was discharged with advice.

So his final diagnosis was Expanded Dengue syndrome with ARDS with Myocarditis with fulminant Hepatic failure with AKI. DHF with ARDS with Myocarditis with Hepatic failure with AKI.

Case II

Mr ZI, a 20-year-old male, was admitted in a private hospital on 25th August with the complaints of fever, bodyache, headache, vomiting and loose motion for 3 days. Patient also

complaints of painful swelling of right leg for 2 days. Fever was high grade continued in nature. He has no rash in the body but subconjunctival hemorrhage. On Examination, the patient was conscious, tachypneic (Respiratory rate-30) toxic and prostrated with moderate dehydration. His pulse was 108/m, BP-100/70 mm of Hg and temperature was 102°F. His abdomen was found soft, moderate tenderness over epigastrium and right hypochondrium, liver was just palpable, on auscultation of abdomen bowel sound found to be increased. Chest examination showed diminished breath sound and dull percussion note in both lower zone. His right leg was found swollen, a bit reddened with Grade 2 tenderness with difficulty in walking. Other systemic examination reveal nothing abnormalities.

On laboratory investigation, ICT for Dengue IgM came positive along with Hb%: 11g/dl, WBC: $7.12 \times 10^9/L$ (Neutrophil: 56%, lymphocyte: 38%) platelet: $137 \times 10^9/L$, HCT- 37.2%, S. bilirubin- 6.10mg/dl, ALT -127 U/L, ALT -160 U/L, S. albumin -2.1, PT with INR: (Control -13.4 s, patient -16.2 s, INR -1.26) APTT: (Control - 30 s, Patient -30 s) S. creatinine - 6.90 mg/dl, Blood urea - 219 mg/dl, CRP - 199 mg/L, S. Amylase - 642 U/L, Serum Lipase-4352, Trop - I - 1525 mg/L. D-Dimer - 11.23, chest X-ray showed bilateral pleural effusion (More in the Right). Hepatitis virology and Serum ANA was found normal.

So, he was diagnosed as a case of 'Expanded dengue syndrome with multi organ involvement (AKI, acute liver injury, pleural effusion, myocarditis, acute pancreatitis) with cellulitis (Right leg)'. The patient was managed in ICU setup with O₂ inhalation (5 L /min) intravenous crystalloid solution and intravenous antibiotics (Piperacillin-tazobactam and Linezolid). Cellulitis was managed by incision and drainage with local anesthesia.

On the 3rd day of admission, the patient developed respiratory distress and chest pain. CXR showed bilateral opaque shadow involving most of the lung field area. His oxygen demand was increasing and SpO₂ maintained 90% with 60L/min O₂ therapy through CPAP. Conscious level was fallen down (GCS-10/15) along with reduced urine output (400cc for last 24 hours).

On 4th day of admission, his renal function was deteriorating further. Hemoadsorption therapy was continued, followed by 4 sessions of heparin free haemodialysis. After hemoadsorption therapy and haemodialysis, patient's oxygen demand and serum creatinine level gradually decreased and both clinical and biochemical conditions improved significantly. Patient was discharged on the 10th day of admission.

Case III

Ms. SA, a 21-year-old female was admitted in the same hospital on September 28, 2023 with the complaints of fever for 5 days along with abdominal pain, vomiting and cough. Here, she was examined clinically and investigated accordingly. Her CBC report on 28.09.2023 showed WBC count- $3.45 \times 10^9/L$, Platelet count- $88 \times 10^9/L$, Haematocrit-36%. Her LFT was normal (S. Bilirubin 0.1 mg/dl, SGPT 57 U/L, SGOT 64 U/L). Her renal function test was almost within normal limit (S. creatinine 1.26 mg/dl). Her IL-6 on 30.09.2023 was 134.5 pg/ml (Reference value upto 7.0 pg/ml).

After two days, the patient developed compensated shock, and fluid was given according to national dengue management protocol. But she didn't improve. Within a short period, the patient underwent decompensated shock which was reversed by giving colloid (Hydroxyethyl starch, Albumin). In the meantime, the patient felt shortness of breath. Patient had a previous history of bronchial asthma. Immediately CXR P/A view, NT-Pro BNP, Troponin-I and ECG were done. CXR showed bilateral opacity. ECG was within normal. Her Troponin-I was within normal limit (<2.50 ng/ml), but her NT-Pro-BNP level was high (1072.1 pg/ml).

On Day-07, her Anti-Dengue Ab IgM and IgG both were both positive. So, it was indicated that this patient had a secondary dengue infection with a cytokine storm. From day 07 patient condition was deteriorating. Patient's Blood pressure became 60/40mm hg. Fluid but oxygen demand was increasing. The patient was levelled as having expanded dengue syndrome with cytokine storm with secondary bacterial pneumonia'. Then heparin free Hemoadsorption therapy was given on 01.10.2023 through femoral catheter. It had a duration of 16 hours, with a blood flow rate of

(100-150) ml/min. Patient's condition improved gradually and was discharged on 08.10.2023 on request.

Discussion

Patients were selected for study after admission in ICU. Patients were admitted in hospital with suspected infection of dengue on the basis of clinical presentation which was confirmed by NS1 Antigen and IgM antibody detection. They were categorized as severe dengue with organopathy (Expanded dengue syndrome) according to pocket guideline of dengue case management, July 2023, where patients of severe dengue were complicated with myocarditis, encephalitis/ encephalopathy, ARDS, acute liver failure and AKI. Patients of expanded dengue syndrome were initially treated with fluid therapy according to protocol to maintain blood pressure, along with intravenous antibiotics and other supportive treatments. When fluid therapy failed, then a vasopressor was added. Patients were given needful oxygen supplement with non invasive ventilation. When all the conventional measures failed, then hemoadsorption therapy was added. The outcome was assessed by clinical improvement of vital signs, biochemical parameters, chest X-ray and ABG.

All three patients were young adults, age <30 years, and had different organopathies, like myocarditis, acute hepatic failure, ARDS, coagulopathy and AKI but there was no comorbidity. hemoadsorption therapy were given early after development of expanded dengue syndrome,

We observed clinical improvement of patients within 48hrs of hemoadsorption therapy. ARDS patients gradually showed a decreased requirement of oxygen. ABG parameter improved and X-ray showed radiological improvement and vasopressor support was withdrawn gradually. Other biochemical and clinical parameters become normal shape. Patients were shifted from the ICU to ward within 4-5 days.

Kogelmann et al. advised to initiate hemoadsorption early. 'hemoadsorption using Cytosorb resulted in rapid hemodynamic stabilization and increased survival, particularly in patients in whom therapy was started early'.¹²

Mehta et al. described hemoadsorption as safe and well tolerated rescue therapy option in patients with septic shock. However, it was recommended that early (Preferably within < 48 h after onset of septic shock) initiation could result in better clinical outcomes.¹³ Sharma et al. also stated that adjuvant hemoadsorption therapy in conjunction with standard treatment and CRRT (Continuous Renal Replacement Therapy) was found to be a safe and effective therapeutic alternative in a patient suffering from septic shock, ARDS and AKI.¹⁴

Cirstoveanu CG et al. reported that hemoadsorption has proven to be a safe and efficacious extracorporeal treatment modality in adults for treating complications of liver failure such as hepatic encephalopathy, hemodynamic instability and progressive hyperbilirubinemia.¹⁵ Tomescu D et al. showed that hemo adsorption using Hemoadsorption has proven to be a safe and improvement of liver function in a patient of acute liver failure.¹⁶

Khan et al. reported on the successful clinical application of extracorporeal hemoadsorption in a case of dengue fever with MODS treated with standard care along with extracorporeal hemoadsorption assist device.¹⁷ Hemoadsorption also used in cardiac surgery. Hemoadsorption therapy, by removing excessive levels of cytokines, may be a solution with the potential to reduce post-operative complications in patients undergoing cardiac surgery.¹⁸

Mariano F et al. showed repetitive use hemoadsorption as an adjunctive therapy for severe burn patients with AKI-CKRT and septic shock was associated with an improvement clinically and a lower mortality rate compared to patients treated with CKRT alone.¹⁹ Mikacic M et al. so expressed their view on effective use of hemoadsorption on rhabdomyolysis patient. Repeated use of hemoadsorption with conventional hemodialysis led to a rapid and sustained decrease in myoglobin and creatinine kinase averting potential damage to the kidneys and other organs.²⁰

However, there is a scarcity of reports on extracorporeal therapy concerning the population in the context of Bangladesh. The pathophysiology

involving a cytokine storm leading to endothelial cell leakage is well established with DF, DHF and DSS. Hemoadsorption therapy modulates the immune response through eliminating excessive cytokine levels.

In these case series, despite all the standard treatment for thrombocytopenia, hyperbilirubinemia and transaminitis, patient's conditions were not improving. However, hemoadsorption was found to be successful and all three patients recovered.

Conclusion

Expanded Dengue Syndrome (EDS) is a new entity incorporated into WHO guidelines on the management of dengue infection. Most of case fatality occur due to Expanded Dengue Syndrome (EDS) when all recommendation fail to save patients. All the patients, in our case series were under thirty years of age. As the patients were relatively young in age and had no co-morbidity and hemoadsorption were given early after development of expanded dengue syndrome, it might have shown excellent outcome.

Recommendation

Large-scale studies should be done to fill the research gap and guide the health authorities to revise the management guidelines of Expanded Dengue Syndrome (EDS) in this regard.

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Contribution of authors

MSA-Concedption, drafting, critical revision & final approval.

MRK-Design, drafting, citing references & final approval.

RDG-Critical revision, citing references & final approval.

Informed Consent

All the 3 patients was informed and consent were obtained about this publication and the necessity of such publication.

Disclosure

All the authors declared no competing interest.

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