A case report to highlight the impact of extracorporeal cytokine elimination therapy in viper snakebite induced septic shock with acute kidney injury

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ABSTRACT — OBJECTIVE: *Snakebite envenomation can lead to prolonged disruption of hemostasis, neuromuscular paralysis, myolysis (muscle degeneration) followed by release of damage associated molecular patterns, acute kidney injury and hypovolaemic shock due to underlying cytokine storm. Extracorporeal cytokine adsorption device can be used to address the cytokine storm.*

PATIENTS AND METHODS: A 40-year-old male patient underwent hypotensive and circulatory shock post viper snakebite making it difficult to maintain mean arterial pressure (MAP) >65 mmHg. Standard of care was ensured. Further, the patient progressed towards septic shock and multi organ failure, starting with acute respiratory distress syndrome followed by acute kidney injury. Inflammatory markers were indicative of cytokine storm. Considering the severity, extracorporeal cytokine adsorption device (CytoSorb) was initiated along with hemodialysis for 8 hours.

RESULTS: Post CytoSorb, noradrenaline dose was reduced and eventually terminated. The ventilation support was weaned. Circulatory shock was restored which was evident by the normalization of hemoglobin, platelet counts and leukocyte counts. Procalcitonin dropped considerably from the baseline. Eventually Sequential Organ Failure Assessment (SOFA) score reduced significantly to 1, which, at the time of admission, was 14.

CONCLUSIONS: Extracorporeal cytokine adsorption device along with standard of care appears a promising approach towards better outcome post snakebite induced multi organ failure.

KEYWORDS
Viper envenomation, Septic shock, Coagulopathy, Acute kidney injury, CytoSorb.

INTRODUCTION

Snakebite remains an important cause of accidental death in modern India, and its public health importance has been systematically underestimated. The estimated total of 45,900 national snakebite deaths in 2005 constitutes about 5% of all injury deaths and nearly 0.5% of all deaths in India[1]. Snakebite envenoming affects people in predominantly poor, rural communities in tropical and subtropical countries throughout the world. There is a strong association between low socioeconomic status or poverty and a high incidence of, and mortality due to, snakebite envenoming[2-5]. Snakes venoms are complex mixtures

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of molecules that induce diverse effects on the human systems (hemorrhage, edema, myonecrosis and bleeding disorders). Envenoming induced by snakebite is characterized by local tissue damage involving hemorrhage, blistering, myonecrosis and inflammation. The inflammatory response has relevance in the evolution of tissue damage; it is associated with edema, pain, leukocyte infiltration and release of several mediators[6].

Viper snake bites are known to cause local complications like necrosis and cellulitis and systemic complications such as coagulopathy, acute renal failure (ARF), and haemolysis[7]. Increase of capillary permeability was reported after snake envenomation leading to the release of several mediators. Many components of snake venoms (phospholipases A2s [PLA2s], bioamines and proteinases) contribute to the induced inflammatory response which is initiated by an increase of vascular permeability followed by cell infiltration[8]. The induced inflammatory response by snake venoms particularly those of *Viperidae*, is amplified by the presence of metalloproteinases, serine proteases, PLA2s and other non-enzymatic proteins such as disintegrins and C-type lectins, which alter the vessel walls and trigger tissue damage[6].

Activation of the complement system results in the formation of many additional degradation products that serve as important mediators of inflammation. Snake venoms stimulate the activation of mast cells which lead to histamine release, inducing vascular permeability and vasodilatation leading to extravasation. Furthermore, the kinin system can also be activated directly by the proteinases of snake venoms that activate the release of bradykinin[9,10]. This system is initiated by activation of Hageman factor (FXII) following tissue injury. This plasmatic factor activates in turn, the prekallikrein into kallikrein, in presence of kininogen, leading to vasoactive peptides causing fever and pain. Bradykinin is a small-peptide responsible for the increased vascular permeability due to its binding with specific receptors on sensory neurons; it, therefore, activates the alternative complement pathway which amplifies the inflammatory response[11]. This vicious cycle of inflammation leads to cytokine storm which further worsens to sepsis with multi organ dysfunction (MODS).

The complexity of the snake venoms and their effects post envenomation makes their treatment difficult. Along with standard of care, it becomes imperative to address the cytokine storm in order to expect a better outcome. The extracorporeal cytokine hemoadsorption device CytoSorb®, containing polystyrene divinyl benzene co-polymer beads with pore size 8-50Å, has been designed to directly capture and reduce mid-molecular weight inflammatory mediators (~10–60 kDa). Pro and anti-inflammatory cytokines, chemokines, and bacterial exotoxins are primarily adsorbed based on concentration gradient manner[11]. Here, we present a case of viper snake bite envenomation with septic shock and acute kidney injury (AKI) treated with standard of care and adjuvant extracorporeal cytokine elimination therapy.

CASE PRESENTATION

A 40-year-old male quadragenarian railway employee encountered snakebite on his right lower limb, which was followed by severe pain, swelling at the bite location along with dyspnea. Subsequently, he was taken to the Godhra Railway Hospital and received treatment symptomatically post, which he was referred to Vadodara Railway Hospital where broad spectrum antibiotics were administered along with single vial of anti-snake venom (ASV) and the patient was further referred to our hospital after 24 hours of the bite.

Upon admission to the Intensive Care Unit (ICU) (Day 2), along with fever, pain, swelling and dyspnea, the patient was gradually progressing towards hypotensive and circulatory shock with mean arterial pressure (MAP) of 53 mmHg, SpO2 coming down to 95% at room air in addition to low hemoglobin levels (from 15 g/dL to 9.75 g/dL), leukocytosis (43200 cells/mm^3) and thrombocytopenia (82000 cells/mm^3).

Standard of care was initiated by administering intravenous (IV) fluids, antibiotic (injection meropenem), andone1 vial of ASV followed by high dose of noradrenaline to normalize the MAP and twenty sequential blood transfusions to address circulatory imbalance. Despite full standard therapeutic measures, the patients' condition worsened with signs of incipient respiratory, renal and hepatic failure.

On Day 3, the patient was clinically and radiologically diagnosed with acute respiratory distress syndrome (ARDS) (P/F ratio: 60) accompanied by oliguria, increasing creatinine (2.3 mg/dL) and total bilirubin levels (2.0 mg/dL, serum glutamic oxaloacetic transaminase [SGOT] 840 U/l, serum glutamic pyruvic transaminase [SGPT] 635 U/l). Arterial blood gas analyses confirmed severe metabolic acidosis (HCO_3:11mmol/l) while inflammatory markers were clearly elevated with a procalcitonin (PCT) of 3 ng/dL and c-reactive protein (CRP)at 600 mg/L suggesting hyperinflammation.

Taking prompt cognizance of the acute respiratory failure, the patient was put on bilevel positive airway pressure (BiPAP) support. To address progressing acute renal failure the patient was put on hemodialysis (Fresenius 4008s) in continuous veno-venous hemodialysis (CVVHD) mode and a single CytoSorb adsorber was additionally integrated into the hemodialysis circuit (post dialyzer) with low dose heparin to regain control of the hyperinflammatory situation (Day 4). The device was run for 8 hours with uniform blood flow rate of 150 ml/min.

Table I. Clinical and laboratory findings.

Parameters	Pre CytoSorb	Post CytoSorb
Hemoglobin (%)	9.7	13.1
Platelet count (cells/mm^3)	61000	132000
Leukocytes (cells/mm^3)	36500	12500
INR	1.45	1.09
MAP (mmHg)	53	>70
PCT (ng/mL)	3	0.6
PaO_2 (%)	60	150
FiO_2 (%)	100	21
Total bilirubin (mg/dL)	2.1	1.0
SGOT (U/l)	840	250
SGPT (U/l)	635	140
Serum creatinine (mg/dL)	2.3	1.1
SOFA score	14	12

FiO_2, fraction of inspired oxygen; INR, international normalized ratio; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Post Cytosorb (Day 5 after snake bite), a significant reduction in the requirement of noradrenaline was noted and could gradually be weaned off in the following hours. This was paralleled by a clear improvement in the MAP indicating hemodynamic recovery. Liver function as well as pulmonary function improved (partial pressure of oxygen [PaO_2] from 60 to 150 mmHg, fraction of inspired oxygen [FiO_2] from 100% to 21%) followed by weaning of the ventilatory support.

Moreover, there was a significant improvement in the renal function particularly increase of in urine output (400 ml/day to 2500 ml/day) and a decrease in creatinine (2.3 mg/dL to 1.1 mg/dL). Therefore, the patient didn't require renal support and the dialysis was weaned off. Further, resolution of circulatory shock was manifested by normalization of hemoglobin, WBC and platelet counts Day 5 onwards (Table 1).

Subsequently, there was a reduction in the hyper inflammatory response, showing marked improvement in the PCT levels. Sequential Organ Failure Assessment (SOFA) score was recorded at 12 which, at the time of admission was 14 and the patient was discharged to ward within 12 hours post CytoSorb where his SOFA score normalized to 1. Eventually, the patient was discharged from the hospital after 3 days post CytoSorb with complete recovery.

DISCUSSION

In India, more than 200 species of snakes have been identified but only 52 are poisonous; the common krait (Bungarus caeruleus), Indian cobra (Naja naja), Russell's viper (Daboia russelii), and saw-scaled viper (Echis carinatus) are the most poisonous ("the big four"). In the Indian setting, almost two-thirds of bites are attributed to saw-scaled vipers, about one-fourth to Russell's viper, and only a small proportion to cobras and kraits[12,13].

Snake venoms contain an array of proteins, toxins and enzymes that may cause coagulopathy, neurotoxicity, myotoxicity, hypotension and tissue necrosis. Therefore, early and aggressive management of snake bite envenomation is imperative to prevent further complications.

Current management of critical snake bite patients involves wound management, identification of snake and administration of ASVs followed by coagulopathy correction and providing organ support systems. Despite the standard of care, some patients progress to shock and eventually die. In such a state of inadequacy, extracorporeal blood purification technologies can play a vital role in regaining control of these patients.

In the present case, standard of care was proving inadequate and no signs of improvement were noted in terms of respiratory, hemodynamic, renal and inflammatory parameters. Due to rapid worsening of the condition along with deranged inflammation, decision was taken to initiate extracorporeal cytokine elimination therapy to combat cytokine storm. CytoSorb, with the elimination of excess of cytokines as well as other metabolites viz. myoglobin, bilirubin etc. stopped the further deterioration of the patient and enabled patient to standard management.

In a previous report by Sathe et al[14], two cases of snake bite (66-year-old male and 55-year-old male) were successfully managed with CytoSorb demonstrating usefulness of CytoSorb with standard of care in patients with snake bite along with shorter ICU stays and better survival.

Large scale studies are warranted to assess the mortality benefit of CytoSorb in critically ill patients due to snake bite envenomation. Therefore, judicious use of such adjuvant therapies in selected and appropriate patients can help the entire medical fraternity to rescue lives which otherwise may seem to be difficult.

Conclusions

Viper venom is known to cause inflammatory cascade resulting in cytokine storm and multi organ dysfunction. Therefore, CytoSorb as an adjuvant therapy, appears to be a promising approach. However larger studies are required to substantiate the outcome observed in this case study.

Conflicts of interest:
The Authors declare that they have no conflict of interests.

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