Case Series

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Redefining the role of therapeutic plasma exchange in complications of *Echis carinatus sochureki* envenomation refractory to anti-snake venom: A case series

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Abstract:

INTRODUCTION: Saw-scaled viper (*Echis carinatus*) belongs to the Viperidae family. Its venom is hemotoxic and contains several small peptides and proteins affecting the coagulation system. Commonly used anti-snake venom (ASV) products in India are reported to be ineffective or less effective in cases with bites by *Echis carinatus sochureki* which are commonly found in desert areas in Rajasthan. Although therapeutic plasma exchange (TPE) has been successful in patients with snakebite envenomation in the past, American Society for Apheresis guidelines 2019 included this indication under category III with grade 2C recommendation.

AIM AND OBJECTIVES: To report the safety and efficacy of therapeutic plasma exchange procedures in the setting of ASV refractory *E. c. sochureki* envenomation.

MATERIALS AND METHODS: Four patients admitted to our institute in 2021 September with an alleged history of snake bites and who underwent at least one cycle of therapeutic plasma exchange were assessed for clinical outcome, laboratory parameters, and blood product consumption.

RESULTS: Three adult patients and one pediatric patient are included in this case series, all of them males. Indication for TPE in one case was suspected diffuse alveolar hemorrhage (DAH), while in all the other cases was thrombotic microangiopathy (TMA). All received a variable number of sessions from 2 to 5 and 1.3–1.5 plasma volume was removed on an average per cycle. The endpoint of TPE was the resolution of DAH in one while a reduction in lactate dehydrogenase and an increase in platelet count was in TMA cases. Consumption of blood products was drastically reduced in all four patients after starting the procedure. All the adult patients fared well on follow-up while the child had developed acute cortical necrosis and was dialysis-dependent. It has been noted in the previous studies too that a subset of snakebite-induced TMA cases was getting converted to chronic kidney disease and becoming dialysis dependent in the long run.

CONCLUSIONS: In regions where ASV treatment failure is very common, therapeutic plasma exchange is a safe and effective complementary treatment modality along with supportive care.

Keywords:

Echis carinatus, plasma exchange, diffuse alveolar hemorrhage, snakebite, thrombotic microangiopathy

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Introduction

India is home to more than 270 species of snakes, of which about 60 are venomous, and snake bites cause around 58,000 deaths

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and 140,000 disabilities every year.[1] Majority of fatal bites in India are due to the spectacled cobra (*Naja naja*), common krait (*Bungarus caeruleus*), Russell's viper (*Daboia russelli*), and Saw-scaled viper (*Echis carinatus*), which are termed the big four dangerous snakes and anti-snake venom (ASV) produced in India is primarily effective against these four species.[2] The saw-scaled viper (*E. carinatus*) belongs to the Viperidae family[3] and is found across the semi-arid regions of Africa, the middle east, and the Indian subcontinent.[4] The Saw-scaled viper venom is hemotoxic and contains several small peptides and proteins affecting the coagulation system.[5] With its potent procoagulant toxins, venom-induced consumptive coagulopathy (VICC) is one of the predominant clinical manifestations of the Saw-scaled viper envenomation.[6-9] Although therapeutic plasma exchange (TPE) has been successful in patients with antivenom refractory snakebite envenomation in the past,[10] American Society for Apheresis guidelines 2019 included "envenomation" under category III with grade 2C recommendation without specifying any genus or species bites.[11] This indicates that there is a shortage of published data on this topic. In this case series, we report four cases of the saw-scaled viper bite envenomation where therapeutic plasma exchange was done as an adjunct to supportive treatment.

Case Reports

Patient 1

A 40-year-old male patient was brought to the emergency room with an alleged history of saw-scaled viper bite on the right foot with pain and swelling extending to the right knee. He was hemodynamically stable on presentation (PR: 92/min, blood pressure [BP]: 110/88 mmHg, respiratory rate [RR]:18/min, temperature: 98.4 F, SpO_2: 99% @ RA). He had received ten vials of ASV from another hospital and ten more vials were received from the emergency room. Over the next 8 days of the course of admission to the hospital, the patient developed gross hematuria, ecchymosis, puncture site bleeding, hematomas in rectus sheath, scrotum, perineum and penis with elevated bilirubin, deranged prothrombin time/international normalized ratio (PT/INR), reduced fibrinogen levels, and prolonged whole blood clotting time (WBCT). Ultrasound kidney, ureter, and bladder revealed clots in the urinary bladder. He received 12 packed red blood cells (PRBCs), 24 fresh frozen plasmas (FFPs), 2 random donor platelets, and 22 cryoprecipitates during these 8 days. The patient started developing respiratory distress, was intubated on day 9 due to progressive tachypnea and desaturation and was suspected of having a diffuse alveolar hemorrhage (DAH). Therapeutic plasma exchange was started on day 9 itself. Although the patient clinically improved after the 1st cycle of TPE, he developed effusion and chest infiltrates after the 2nd cycle (day 11). A total of four cycles of therapeutic apheresis were done (days 13 and 15). Details of each cycle are given in Table 1. The coagulation profile was improved, and INR was normalized after the day 16. The patient then developed hypofibrinogenemia and started on cryoprecipitate transfusion. On the following days, there were episodes of decrease and increase in the size of rectus sheath hematoma, which were managed with further blood transfusions. Five PRBCs and 30 cryoprecipitates were transfused post plasma exchange. The patient was finally discharged with stable vitals.

Patient 2

A 50-year-old male presented to our hospital with an alleged history of snakebite over his right foot at his farm and received 20 vials of ASV from outside. At presentation, the patient had right lower limb swelling extending up to the knee joint, a WBCT of more than 20 min, and bleeding from the gums. D-dimer was elevated, deranged renal function tests and PT/INR were there, and a partial thromboplastin time was >120 s. The patient was suspected of having thrombotic microangiopathy (TMA) and VICC. Three cycles of therapeutic plasma exchange on alternate days, started on the 9th day of admission, with FFP as replacement fluid and multiple cycles of hemodialysis and other supportive management were done. Mild hematuria persisted even after the cessation of the 3rd cycle, and the patient gradually improved over the next 10–15 days without any active intervention. The patient was discharged on improving renal function tests.

Patient 3

A 10-year-old male child presented with an alleged history of snakebite on the left hand while playing on the ground. The child was initially taken to a local hospital, where he received 15 vials of ASV. On presentation, vitals were stable PR: 110/min, RR: 40/min, temperature: 98.6 F, SPO_2:94%. The child received 20 more vials of ASV at our emergency room. WBCT was >20 min and persisted even after maximum ASV administration. Consumptive coagulopathy was suspected given deranged PT/INR and persistently elevated D-dimers. The patient developed a compartment syndrome and a fasciotomy was done. There was a sharp drop in hemoglobin (from preoperative 13.5 to 3.2 g/dl), and 1 PRBC was transfused for the same. Because of severe anemia and decreased urine output, the patient was shifted to the pediatric intensive care unit. A dipstick test was done given hematuria and was suggestive of hemoglobinuria. The patient remained anuric despite the fluid challenge. ISTH scoring

was done and was suggestive of overt disseminated intravascular coagulation (DIC). Peripheral blood film revealed 3% schistocytes with markedly elevated lactate dehydrogenase (LDH), and the possibility of TMA with DIC was considered. The first cycle of therapeutic plasma exchange was started on the 5th day of the presentation. Five cycles were done almost daily with FFP as replacement fluid with daily monitoring of hemolytic and DIC parameters. The child showed a response in improved coagulation parameters, LDH, and improved kidney function tests. Anuria persisted, which started improving trend 1 week after getting shifted from pediatric intensive care unit. The child had received three PRBC, three cryoprecipitates, and four FFP units during the stay, in addition to plasma exchange. On follow-up, the patient was dependent on dialysis, and acute cortical necrosis was noted on renal biopsy.

Patient 4

A 45-year-old male patient presented with an alleged history of snakebite on the right foot 3 days back, followed by pain, redness, and swelling at the bite site. On presentation, vitals were stable PR: 74/min, BP: 124/76 mmHg, RR: 18/min, temperature: 98.7 F, investigations revealed a fall in hemoglobin, peripheral blood smear showed 3%–4% schistocytes, low fibrinogen levels, elevated D-dimers, and deranged renal function tests. The patient was diagnosed with TMA and DIC. The patient had decreased urine output and persistent metabolic acidosis during the hospital stay. The patient underwent hemodialysis. Ten units of cryoprecipitate were transfused, and two cycles of therapeutic plasma exchange on alternate days with FFP as replacement fluid were also done. The patient was started on prednisolone given suspected atypical hemolytic uremic syndrome. The patient improved clinically, urine output improved and maintained stable vitals 2 days procedurepost. The patient was discharged in stable condition and with renal function tests on an improving trend.

Demographic data, indication, procedure details, and theoutcome of each patient are summarized in Table 1.

Discussion

E. c. sochureki is the *Echis* subspecies commonly found in Rajasthan.[9] Owing to its regional variations in the composition of toxins in the venom, polyvalent ASV widely used in India is relatively less effective in sochureki bites than bites from other *Echis* subspecies in India.[12] In a study comparing the composition of toxins in the venom from *Echis* sp. From three different geological regions in India, *Echis* venom from Rajasthan differed from that of Tamil Nadu and Goa in having a predominant Phospholipase A2 and P-II Snake Venom Metallo-proteinase (svMP) composition. Phospholipase A2 has many effects, including myotoxicity, cardiotoxicity, hemolysis, and

Table 1: Summary

Age	Sex	Number of cycles	Indication	Frequency	Replacement fluid	Outcome	Follow-up
40	Male	4	DAH	Alternate	Only FFP	DAH resolved; chest signs improved; extubated	Uneventful
50	Male	3	TMA	Alternate	NS + FFP	LDH, platelet count improved	Uneventful
10	Male	5	TMA	Daily	NS + FFP	LDH, platelet count improved	Acute cortical necrosis, dialysis-dependent
45	Male	2	TMA	Alternate	NS + FFP	LDH, platelet count improved	Uneventful

DAH=Diffuse alveolar hemorrhage, TMA=Thrombotic microangiopathy, LDH=Lactate Dehydrogenase, NS=Normal Saline, FFP=Fresh Frozen

Table 2: Review of literature: TPE in snakebite

Article	Author	Published on	Number of patients	Snake species	Diagnosis	Outcome
CR	Cobcroft *et al*	1997	1	Taipan	HUS	Expired
CS	Yildirim *et al*	2006	16	Unknown	Not subcategorised	Recovered
CS	Isbister *et al*	2007	6	Brown snake	TMA	All recovered
CR	Keyler *et al*	2008	1	lowland viper	TMA	partial recovery
CS	Casamento *et al*	2011	2	Tiger snake	TMA	partial recovery
CS	Zengin *et al*	2013	37	Several species	Not subcategorised	Recovered
CR	Withana *et al*	2014	1	Hump nosed viper	TTP	Recovered
CS	KSV Godavari	2016	2	Unknown	HUS	Recovered
CS	Dhineshkumar *et al*	2017	2	Russel's viper	TMA	CKD (50% patients)
CR	PR Murthy *et al*	2019	1	Unknown	TTP	Recovered
CR	Obeidat *et al*	2020	1	Echis coloratus	TMA	Recovered
CR	P Arora *et al*	2020	1	Russel's viper	TMA	Recovered
CS	Senananda *et al*	2020	17	Viper	TMA	CKD (50% patients)
CS	M Kumar *et al*	2021	2	Unknown	TMA	Recovered

TMA=Thrombotic microangiopathy, HUS=Hemolytic Uremic Syndrome, TTP=Thrombotic Thrombocytopenic Purpura, CKD=Chronic Kidney Disease, TPE=Therapeutic Plasma Exchange

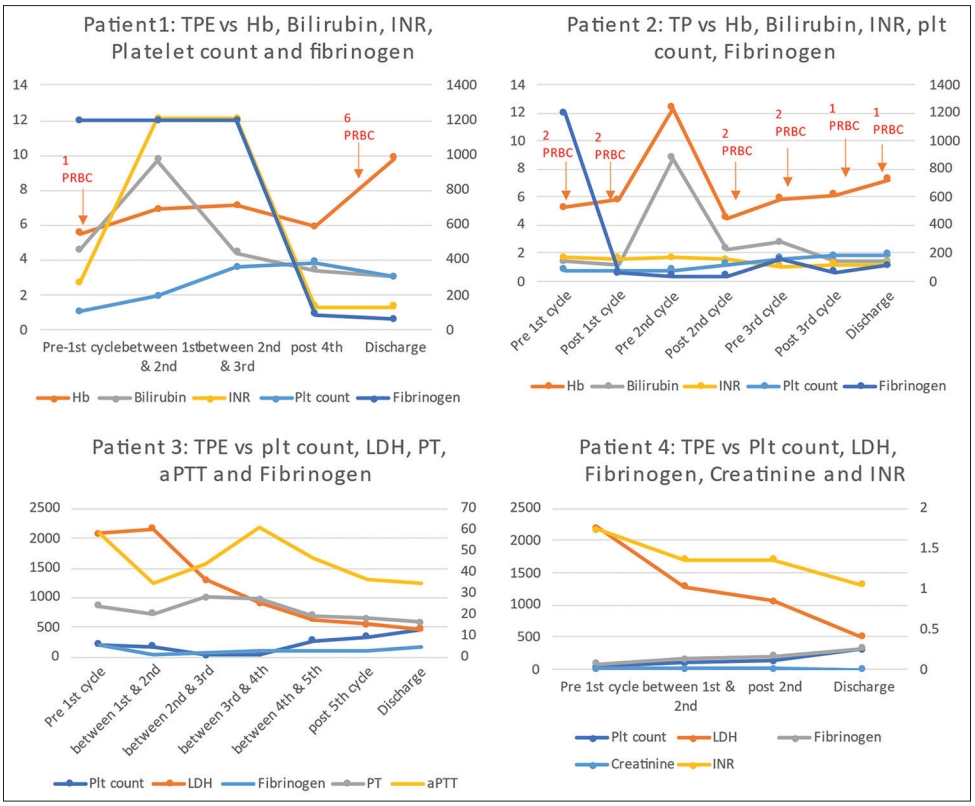

Figure 1: Trend of lab parameters versus TPE in each patient. TPE = Therapeutic Plasma Exchange, Hb=Hemoglobin, INR = International normalized ratio, LDH = Lactate dehydrogenase, PT = Prothrombin Time, aPTT = activated Partial thromboplastin time

hemorrhage, while svMP facilitates other toxins' entry by breaking extracellular fibrinogen and basement membrane, leading to bleeding.[13]

Within the genus *Echis*, several prothrombin activators have also been demonstrated, catalyzing prothrombin into thrombin and leading to microthrombi formation.[14] In its usual prey, this will cause intravascular coagulation and cardiac arrest or death. However in humans, due to dilution in a large blood volume, these numerous microthrombi will consume most of the coagulation factors and platelets, a phenomenon known as VICC.[15,16] The inter- and intraspecific variations in the composition of venom in *Echis* sp. is well documented, which can also affect the susceptibility to ASV.[17,18] ASV is polyvalent serum directed against the venom from a specific region, leading to treatment failures in snake bites from another region. Two polyvalent antivenoms developed from *E. carinatus* of the Chennai population failed to neutralize *Echis* venom from another unknown region in India.[14] There are case reports available where *E. c. sochureki* bites from Rajasthan failed to respond to polyvalent antivenom prevalent in India.[9,19]

Although there are no controlled trials to substantiate the efficacy of therapeutic plasma exchange in snakebite envenomation, in the case of *E. sochureki* bites, where anti-venom treatment failure is common, in states like Rajasthan, plasma exchange may have a role if timely performed. Since, in most human studies, the distribution of snake venom is hypothesized as a one-compartment model and has an intravascular half-life not more than 2 days,[20] plasma exchange can remove these toxins and prevent further end-organ damage, even though an optimal time for initiation of plasma exchange has not been mentioned in any of the guidelines we have come across. It also replaces the coagulation factors consumed in VICC if FFP is used as the replacement fluid. In the present case series, even in patients where plasma exchange was initiated late, it could prevent catastrophic bleeding by replacing the coagulation factors without causing volume overload in the anticipated event of a massive transfusion. Most of the laboratory parameters have improved in all four patients, as per the graphs [Figure 1]. Multiple case reports showed improvement in laboratory parameters and overall clinical outcome post TPE in snake bite patients. TPE was suggested as a complementary treatment modality by some of the authors.[10,21-23]

In the present case series, three adult patients and one pediatric patient are included, all-male. *E. c. sochureki* subspecies were identified in all four cases from the photographs produced by the patient attendants taken after killing the snakes. All procedures were done in Spectra Optia (Terumo BCT) centrifugal apheresis

machine with ongoing calcium infusion titrated as per the pre-procedure ionized calcium levels. Indication for TPE in one case was suspected DAH, while in all three other cases was TMA. All received a variable number of sessions from 2 to 5, and 1.3–1.5 plasma volume was removed on average per cycle. The frequency of cycles was mostly alternate days except for the child who had daily procedures. Choice of replacement fluid was only FFP in the DAH patient, whereas a combination of NS + FFP was used in all others. The endpoint of TPE was defined as the resolution of DAH in one patient while reducing LDH and increasing the platelet count in TMA cases. After starting the procedure, the consumption of blood components was decreased in all four patients. Anuria in the child and hematuria in two patients persisted for at least a week after cessation of plasma exchange. The fourth patient had only microscopic hematuria, which got resolved post procedure. All the adult patients fared well on follow-up, while the child had developed acute cortical necrosis and was dialysis-dependent. It has been noted in the previous studies, too, that a subset of snakebite-induced TMA cases was getting converted to chronic kidney disease in the long run.[24-26] It is to be noted that antivenom is still the primary treatment modality in suspected snakebite patients, and plasma exchange was used as a supportive measure here as antivenom was not working.

Reviewing the literature, we found only case reports where plasma exchange was used as an adjunct in snake bite patients and summarized in Table 2.

Conclusions

In regions where anti-venom treatment failure is expected, therapeutic plasma exchange can be safely used as a complementary treatment modality along with supportive care. Controlled trials should be conducted to test the safety and efficacy of plasma exchange in these envenomation patients, which may help to generate enough data to support its routine use.

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Conflicts of interest
There are no conflicts of interest.

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