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The Use of Therapeutic Plasmapheresis in the Treatment of Poisoned and Snake Bite Victims: An Academic Emergency Department's Experiences

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The objective of this study is to describe the clinical status, procedural interventions, and outcomes of critically ill patients with poisoning and snake bite injuries presenting to a tertiary-care emergency department for treatment with therapeutic plasmapheresis. Records of 20 patients who presented to our academic emergency department over a 2-year period and who underwent plasmapheresis for poisoning or snake bite were retrospectively reviewed. Plasmapheresis was performed using centrifugation technology via an intravenous antecubital venous or subclavian vein catheter access. Human albumin or fresh frozen plasma were used as replacement fluids. Data extracted from the patient record included demographic data, clinical status, and outcome measures. Sixteen patients underwent plasmapheresis because of toxicity from snake bite. Three patients were treated for drug poisoning (phenytoin, theophylline, bipyridene HCl) and one patient for mushroom poisoning. Haematologic parameters such as platelet count, PT, and INR resolved rapidly in victims of snake bite injuries after treatment with plasmapheresis. Loss of limbs did not occur in these cases. Seven patients required admission to the intensive care unit. One patient with mushroom poisoning died. Mean length of hospital stay was 14.3 days (range 3–28 days) for all cases. Plasmapheresis was a clinically effective and safe approach in the treatment of snake bite envenomation and other drug poisoning victims especially in the management of hematologic problems and in limb preservation/salvage strategies. In addition to established conventional therapies, emergency physicians should consider plasmapheresis among the therapeutic options in treatment strategies for selected toxicologic emergencies. J. Clin. Apheresis 2006.

Key words: plasmapheresis; drug poisoning; snake bite

INTRODUCTION

Plasmapheresis is a nonspecific extra-corporeal blood cleansing treatment used in many immunologic and toxicologic disorders [1–4]. Although the clinical application of plasmapheresis may be declining in some established areas, other new or expanded uses for it in strategies for drug and poison detoxification have increased, for example, in the treatment of the intoxications with drugs that are highly protein bound or those that have a prolonged plasma half-life.

Although a role for anti-venom therapy, as well as supportive care are critical for successful treatment in such settings, the prognosis in snake bites and drug poisonings may be improved by the rapid removal of toxins. Such methods include oral activated charcoal, forced diuresis, peritoneal dialysis, hemodialysis, and charcoal hemoperfusion [5,6].

Although many snakes are harmless, some families of snakes, such as Elapidea, Viperidea, Hydropidae, Colubridae, and Crotalidae, are dangerous to humans [7]. In Turkey, the most dangerous snakes are the *Vipera ammodytes meridionalis* ("boz yılan" in Turkish), which are found in the eastern and southern parts of the country. Snake bite injuries usually occur in rural areas, most often in the summer months.

Snake venoms consist of low molecular weight peptides and enzymes that have hematotoxic and neurotoxic properties. In 20–30% of patients with clinical symptoms and signs after snake bite (the others being "dry" bites), hematological abnormalities such as disseminated intravascular coagulation (DIC) and other bleeding (i.e., gastrointestinal, nasal, oral, genitourinary, and dermal), may occur [8,9].

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Additionally, many venoms also have cytotoxic effects that lead to tissue necrosis. With improper treatment, patients risk loss of an extremity or death.

Currently, the mainstay of treatment for snake bite and poisoned patients remains aggressive supportive care in hospitals. Plasmapheresis is considered by the American Society for Apheresis (ASFA) to be a Category II therapy for the treatment of drug intoxications, but to date plasma exchange therapy has not been listed as being useful in the treatment of snake bite patients [10].

Here we report our experiences in the treatment of various drug intoxications and snake bite injuries in a hospital emergency department setting.

MATERIALS AND METHODS

Approval from the university's institutional review board was obtained for collecting demographic and clinical data on Emergency Department patients undergoing therapeutic plasmapheresis for poisoning. All patients undergoing plasmapheresis for the treatment of poisonings and snake bites presenting to the Emergency Department of our tertiary university hospital between January 2002 and December 2004 were included in this retrospective descriptive study. The Emergency Department receives approximately 35,000 patients annually for evaluation and treatment. The following data were recorded: demographic characteristics (i.e., sex, age), selected details of the history (e.g., toxin exposure such as drug overdose and/or chemical agents, the site of the bite), clinical findings, blood test results, treatments rendered, and selected clinical outcomes (e.g., mortality, seizure, length of stay, ICU admission).

The decision to perform plasmapheresis in patients with acute drug poisoning was based on the responsible agent's (i.e., toxic substance) capability of binding to plasma proteins, its half life, volume of distribution, and elapsed time since the patient's initial exposure [6]. Apheresis was performed using a Haemonetics 3p® pheresis machine (Braintree, MA). At least one plasma volume was exchanged in all patients. Human albumin was used as a replacement fluid in the majority of cases, but fresh frozen plasma (FFP) was used in some cases, especially for those patients in hepatic failure. Patients were treated in either the intensive care unit (ICU) or the emergency department observation unit.

Statistical Analysis

The paired simple t-test was used to analyze differences (pre- and post-plasmapheresis) in various hematology parameters including platelet count, partial thromboplastin time (aPTT), international ratio (INR), and protrombin time (PT). Data are expressed as the mean ± SEM (Standard Error Mean) with $P < 0.01$ considered statistically significant for all comparisons.

RESULTS

Of 30,605 admissions to our Emergency Department between January 2002 and December 2004, 216 (0.7%) were due to toxicologic causes. Patients, aged 16 to 25 years, accounted for the largest number of cases. Most of the patients admitted to the ED were females (68.8%). Twenty patients presented with poisoning during the 2-year study period, of whom 12 (60%) were female. The median age was 44.85 years (range, 13–72). All of the patients underwent at least one session of plasmapheresis. Sixteen patients had been bitten by poisonous snakes, three had severe poisoning from various therapeutic agents (phenytoin, theophylline, bipyridene HCI), and one had mushroom poisoning. Seven patients needed assisted ventilatory support and were transferred to the ICU after initial stabilization in the Emergency Department. Only one patient died secondary to the development of liver failure and brain edema after mushroom poisoning. Adverse reactions related to the apheresis intervention were observed in two patients (one with mushroom, another with theophylline poisoning) who received FFP during plasmapheresis. Those reactions did not result in cancellation of the procedure. The average number of plasmapheresis sessions was 1.9 per patient. The average length of hospital stay for all patients was 14.3 (3–28) days with victims of snake bites having slightly longer hospitalizations (mean = 16.6 days) (Table I).

Most of the snake bites were to the ankle or hand areas, but one patient was bitten on the face (Fig. 1a,b). Hematologic results are given in Table II. Only one snake bite patient, the individual bitten on the face, had difficulty breathing and was intubated and placed on ventilator support. Extremity damage necessitating amputation did not occur in any patient. Data from the four non-snake bite patients are shown in Table III.

DISCUSSION

Patients with immunologic disorders and toxicological exposures who respond poorly or are unresponsive to conventional therapy may recover after being treated with plasmapheresis [4]. A variety of medical conditions have been treated with plasmapheresis [1]. With respect to the removal of toxic substances from the blood, plasmapheresis may offer

TABLE I. Demographic and Clinical Characteristics of Snake Bite Patients*

Patient no.	Age (years)	Sex	Bleeding	ICU admision	Ventilator required	Hospital stay (days)	Site of snake bite injury
1	21	F	Subcutaneous	−	−	14	Left hand
2	53	F	Subcutaneous	−	−	13	Right hand
3	50	F	Subcutaneous	−	−	20	Right hand
4	34	M	Subcutaneous	−	−	14	Left hand
5	17	M	Subcutaneous	+	−	27	Ankle
6	70	M	Subcutaneous	+	−	14	Right hand
7	28	M	Subcutaneous	−	−	12	Ankle
8	13	F	Subcutaneous, mucosal, gingival, nasal, tracheal	+	+	28	Face
9	25	F	Subcutaneous	−	−	13	Right ankle
10	16	M	Subcutaneous	+	−	21	Right ankle
11	72	F	Subcutaneous	−	−	10	Right gluteus
12	60	F	Subcutaneous	−	−	10	Left ankle
13	66	M	Subcutaneous	+	−	25	Right hand
14	61	F	Subcutaneous	−	−	18	Right ankle
15	41	F	Subcutaneous	−	−	10	Left ankle
16	75	F	Subcutaneous	−	−	18	Right ankle

*F, female; M, male.

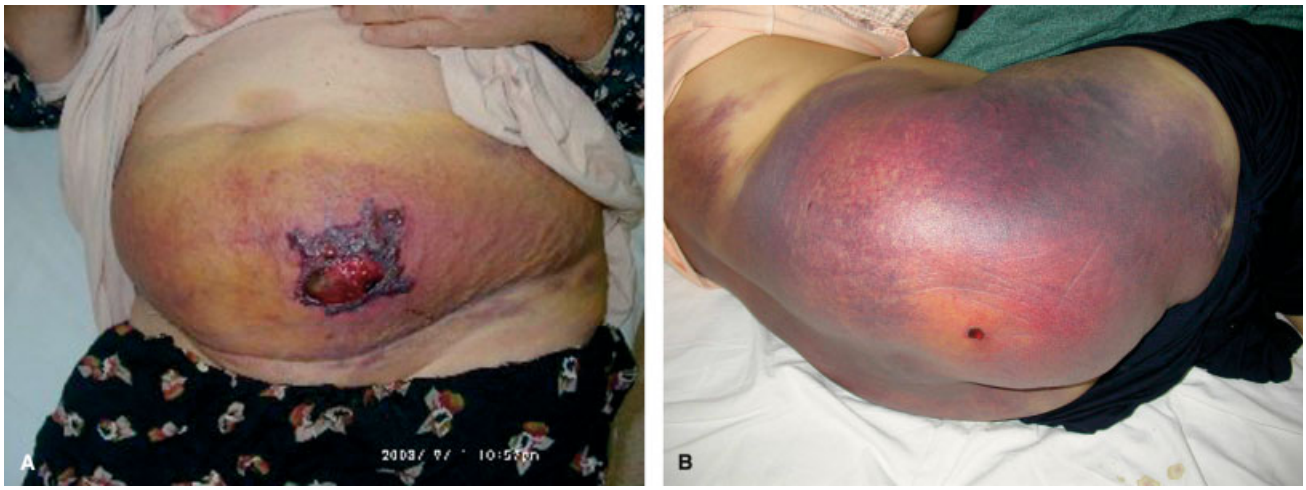

Fig. 1. Examples of snake bite wounds. **A**: Infected open wound on the abdomen with subcutaneous ecchymoses. **B**: Subcutaneous hematoma on the gluteal area.

TABLE II. Hematoloigic Parameters in Snake Bite Patients Before and After Plasmapheresis*

	Before plasmapheresis	After plasmapheresis	*P*
Platelet ($\times 10^9$/L)	75.75 ± 88.40	242.81 ± 80.82	< 0.001
PT (sec)	18.2 ± 6.3	13.2 ± 1.1	> 0.001
INR	1.51 ± 0.74	1.09 ± 0.08	> 0.001
aPTT (sec)	25.0 ± 3.1	27.3 ± 2.8	> 0.001

n = 20; values are mean ± 1 SEM. PT: prothrombin time, INR: international normalization ratio, aPTT; activated partial thromboplastin time.

a rapid strategy for partial or complete removal of various injurious agents [1,2]. Plasmapheresis in snake bite victims to eliminate venom toxins from blood may also be of benefit [11]. Venoms that have diffused out of the blood compartment may not be effectively removed; however, redistribution and elimination of venom toxin from the extra-vascular space and target tissues may occur with apheresis.

Clearance of drugs by plasmapheresis is most effective for toxins that are highly bound to plasma proteins and that also have a low volume of distribution in the body [3]. Plasmapheresis is effective in the treatment of life-threatening intoxications with tricyclic (amitriptyline) and tetracyclic (maprotiline) antidepressants [1]. Although the efficacy of oral activated charcoal in acute theophylline poisoning is well documented, intractable vomiting, paralytic ileus, and depressed levels of consciousness limit its usefulness. Although plasmapheresis for the extra-

TABLE III. Clinical Charateristics of Patients Poisoned by Medications

Patient no.	Age	Agent	Intent	Hypotension	Clinical signs	ICU admission	Ventilation required	Total length of stay (days)	Dead
1	31	Phenytoin sodium	Sulcide attempt	+	Nystagmus	–	–	3	–
2	55	Theophylline	Overrmedication	–	Tachycardia, Flushing, Cough	–	–	7	–
3	39	Bipyridene	Suicide attempt	–	Delirium, Agitation	+	+	7	–
4	70	Mushroom	Accidental	+	GI Bleeding, Lethargy	+	+	3	+

corporeal removal of theophylline has been described, charcoal hemoperfusion has been recommended in severe theophylline poisoning when the serum concentrations are >80 mg/L, or if signs of severe clinical toxicity are present (status epilepticus, circulatory failure, or coma) [6,12,13]. Our patient with theophylline toxicity had seizures and a toxic serum concentration of 40.1 mg/dL. His clinical status resolved and blood theophylline levels were reduced to 8 mg/dL after treatment with plasmapheresis.

In one of our patients, after a single plasmapheresis session, a 63% reduction in the plasma level of amitriptyline was obtained. Other drugs such as verapamil, theophylline, diltiazem, and carbamazepine, as well as heavy metals (mercury and vanadate) are also effectively removed by plasmapheresis [12–15]. Organophosphates, a common intoxication in Turkey, are not removed effectively. Plasma concentrations of dimethoate in two of our patients did not significantly decline with plasmapheresis.

Plasmapheresis has also been used in the treatment of phalloid mushroom intoxication. In this potentially fatal intoxication, for which no antidote therapy exists, plasmapheresis is at least as effective as hemoperfusion in reducing mortality from as high as 30–50% with conventional therapy, to less than 20%. Unlike charcoal hemoperfusion, plasmapheresis does not cause significant thrombocytopenia or hypoglycemia, but potential changes in a patient's electrolyte and volume status must be monitored carefully. Both plasmapheresis and charcoal hemoperfusion expose the patient to risks inherent in any technique that uses an extracorporeal circuit [16]. Plasmapheresis in our study was performed by the veno-venous technique in all patients and few adverse reactions were noted.

Successful applications of plasmapheresis in the case of snake bite victims has been previously noted, [11,17]. Rasulov and Berdymuradov reported on the use of plasmapheresis in 24 patients with poisonous snake bites all of whom recovered and were discharged from the hospital [11]. In their study, similar to ours, however, there are no patient control groups to compare with the plasmapheresis treatment group [11]. In contrast to the previously cited successes, no benefit of plasmapheresis was observed in three patients who were bitten by Malayan krait (*Bungarus candidus*) snakes [18]. This failure may be due to the rapid dissemination of the neurotoxic effect of venom. [18]. Other case reports support the efficacy of plasmapheresis in the treatment of envenomations including patients with coagulopathies [19,20]. Despite a lack of an adequate control group, we believe that reduced hospital stays, minimal adverse complications, and the potential for salvage of limbs in victims of snake bites support the early use of plasmapheresis in such settings.

One patient in our series exhibited visual problems, which resolved after plasmapheresis. Snake venom may also affect the haematologic, neurologic, renal, and cardiovascular systems. Signs may include diplopia, visual defects, and airway problems such as difficulty swallowing and opening of the mouth [21–23]. Monovalent horse antivenom therapy is generally used to treat snake bites in Turkey, but if the type of snake is not known, as generally is the case, specific anti-venom serum cannot be given. Antivenom produced from sheep is less allergic than that from other sources but its availability may be a problem (not available in Turkey) [24]. Enzymes and low molecular weight peptides in the snake venom can also cause problems leading to coagulopathy [8,19–21]. Neutralization of these peptides and enzymes with antivenom is generally warranted, because selective elimination of these molecules has proved impossible. In this regard, previous case reports support the efficacy of plasmapheresis in the treatment of envenomations including patients with coagulopathies [17,19,20]. Beneficial effects of plasmapheresis in the patients presented here may also be due to the elimination of these inflammatory peptides. Rapid improvements in selected laboratory parameters (e.g., PT, INR, and especially platelet count) after plasmapheresis in the patients reported here may further indicate the beneficial effects of this intervention.

From our experiences reported here, plasmapheresis appears effective in limb salvage strategies and management of hematologic problems encountered in snake bite envenomation victims and in other selected drug poisoning (phenytoin, theophylline, bipyridine) situations. If available, plasmapheresis should be

considered as part of an early treatment strategy along with conventional measures in the care of such patients.

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