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Plasma exchange as a complementary approach to snake bite treatment: An academic emergency department's experiences

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ABSTRACT

Snake bites are leading causes of morbidity and mortality worldwide, especially in rural areas. Therapeutic plasma exchange has been used in the treatment of many different conditions such as immunologic diseases, toxicologic disorders, and snake envenomation. The aim of this study is to evaluate the efficacy of plasma exchange treatment on clinical status, outcomes, and discharge of patients who were bitten by venomous snakes. The study was conducted retrospectively in the Emergency Department of Gaziantep University from January 2002 to December 2011. Thirty-seven patients were included in the present study. Routine biochemical and hematologic laboratory parameters were studied before and after plasma exchange. Demographic data, clinical status, and outcomes of patients were recorded. Plasma exchange was performed by using centrifugation technology via an intravenous antecubital or subclavian vein catheter access. Human albumin/fresh frozen plasma was used as replacement fluids. A significant correlation was seen between therapeutic plasma exchange and improvement of laboratory results. None of the study patients lost their limbs. Eight patients were sent to the intensive care unit. The mean length of the hospital stay was 12.2 days (4–28). All patients were discharged with good recovery. No complications were seen during the 3 months following discharge. Plasma exchange appears to be an effective treatment intervention for snake bite envenomations, especially in the management of hematologic problems and in limb preservation/salvage strategies. In addition to traditional treatment methods, plasma exchange should be considered by emergency physicians in cases of snake bite envenomation as a therapeutic approach to facilitate rapid improvement.

1. Introduction

Plasma exchange is a nonspecific extracorporeal technique that removes offending plasma components such as metabolites, inflammatory factors, and toxic mediators, or toxins that are responsible for physical or metabolic disease. Recently, the clinical applications of plasma exchange are increasing, particularly as a method of detoxification in poison and drug cases [1–5]. Antivenom and supportive cares have been used for many years for the effective treatment of poisoning due to snake bites; however, the prognosis in snake bite cases may be improved by the rapid

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and exact removal of the venom. Although plasma exchange is a widely used intervention in immunologic and toxicologic disease states, little data literature exists on its effects on snake bite envenomation.

Snake bites are common in many regions of the world, particularly in rural areas, and injuries occur most often in the summer months. More than 2.5 million people are bitten by snakes each year, resulting in about 100,000 deaths and 400,000 amputations [6,7]. While most snake bites are harmless and tend to be milder, the bites of some snake species in the Elapidae, Viperidae, Hydropidae, Colubridae and Crotalidae families are dangerous to humans [7]. In many regions of Turkey, there are many different snake species. The southeast region of Turkey is home to venomous snakes of the Viperidae family, which include Vipera ammodytes meridionalis ("boz yılan" in Turkish) the most dangerous species [5,8].

The venom of many species consists of carbohydrates, lipids, amines, enzymes, and nontoxic and toxic proteins that have hematotoxic and neurotoxic properties [5,9]. Coagulopathy after snake bite envenomation is a serious medical problem. Snake venom proteins from eight protein families were found to interfere with the hemostatic system at many different points [10]. These proteins decrease the coagulability of blood, induce bleeding and secondary effects thereof, for example hypovolemic shock and organ damage, or induce thrombosis. In addition, many snake venoms may cause tissue necrosis owing to cytotoxic effects [5–7].

Traditional management of snake bites consists of aggressive supportive care (fluid replacement, analgesia, antibiotic therapy, extremity elevation) and antivenom therapy that is the mainstay of treatment. Recently, plasma exchange is considered by the American Society for Apheresis (ASFA) to be a Category III, recommendation grade 2 C therapy for treatment of snake bite envenomation (Category I: standard and accepted as first-line therapy; Category II: generally accepted, supportive to other therapies; Category III: optimum role of apheresis therapy is not established or reported, evidence is insufficient, favorable anecdotal reports conflicting results of trials; Category IV: available controlled trials have shown lack of therapeutic efficacy) [11].

In this paper, we describe our plasma exchange experiences in the treatment of snake bite envenomations in a tertiary-care Emergency Department on the basis of a retrospective study.

2. Materials and methods

The study was conducted in the Emergency and Hematology Departments of Gaziantep University, Turkey from January 2002 to December 2011. Each year, approximately 50,000 patients (>16 years old) refer to our Emergency Department for diagnosis and treatment. Of these patients, approximately 20 are admitted each year due to snake bite. The records of all patients that were bitten by snakes were checked retrospectively. Plasma exchange therapy indication was clarified as being selected for patients whose extremity swelling increased/did not regress, whose circulation was impaired, whose thrombocytopenia did not resolve, and whose International Normalized Ratio increased despite snake antivenom therapy and supportive care. The patients who recovered with antivenom and supportive treatment were excluded from the study. Plasma exchange therapy was completed when extremity swelling, thrombocytopenia decreased/regressed, and International Normalized Ratio came to normal level.

Gender, age, site of the bite, sites of the bleeding, clinical findings, blood test results, total plasma exchange sessions, treatment doses of antivenom, complications, treatments rendered, and clinical outcomes (e.g., length of stay, ICU admission, ventilator required) for all patients were recorded. Plasma exchange was performed by using a Haemonetics MCS 3P® or Fresenius COM. TEC® apheresis machine. Fresh frozen plasma (FFP) or human albumin was used as a replacement fluid in all patients. Between 1 and 4 plasma exchange sessions were performed for each patient. Patients were treated and followed in the Emergency Department or intensive care unit (ICU).

Thirteen patients of current study were reported in another our study at 2006 [5].

2.1. Statistical analysis

SPSS for Windows, version 18.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical evaluation. The differences in various hematology parameters, including platelet count partial thromboplastin time (aPTT), international normalized ratio (INR), and protrombin time (PT) were analyzed by using paired sample *t*-test. The value of $p \leqslant 0.01$ was accepted as statistically significant.

3. Results

Of 450,670 admissions to our Emergency Department between January 2002 and December 2011, 204 (0.045%) were due to snake bites. Of these patients ($n = 204$), 167 recovered with supportive care and antivenom therapy. This group was excluded from the study. Thirty-seven patients who did not recover with aggressive supportive care and antivenom therapy were included in our study (56.8% male, 43.2% female). Of these patients, 11 were admitted to the Emergency Department directly; 24 patients were referred to our hospital for further investigation after their symptoms worsened. These patients were given antivenom and supportive treatment for 5.7 ± 1.6 (3–9) days before being referred to our hospital. All patients included in the study were given antivenom and supportive treatment for 5 ± 1 (2–6) days before performing plasma exchange. The mean ages of all subjects were 43.8 ± 18.5 years (13–79). Eight patients were admitted to the ICU after initial stabilization in the Emergency Department, and two of them needed assisted ventilatory support. The average number of plasma exchange sessions was 2.1 (1–4) per patient. In each session, the replacement fluid used was 14.2 ± 1.7 (12–18) packed FFP (each packed FFP is approximately 200–250 ml in volume) or 7 ± 0.8 (6–8) 20% albumin solution, and mean duration of plasma exchange sessions was 97.1 ± 13.8 min for plasma and 52.3 ± 5.8 min for human albumin. Each 20% albumin solu-

tion is 100 ml in volume and diluted with 400 ml 0.9 % of isotonic saline solution.

When plasma exchange was repeated, it was with daily intervals. We usually preferred to use FFP owing to hepatic and coagulation abnormalities developed due to snake bite, but when FFP did not supplied by the blood bank we had to use albumin for plasma exchange. We did not observe clinically any difference between the usage of albumin and FFP. Adverse reactions related to the plasma exchange intervention were not observed. Hematologic parameters and swelling in the extremity of the patients improved within 3 ± 1 (2–5) days after plasma exchange therapy. The average length of hospital stay was 12.2 (4–28) days. The majority of the snake bites were to the lower extremity (51.4%) and the upper extremity (45.9%) (Fig. 1). One patient was bitten on the face (2.7%). None of the patients needed fasciotomy or extremity amputation. All patients were discharged with good recovery. No complications were seen during the 3 months following discharge. Table 1 depicts, for each patient, age, gender, hospital stay, site of bleeding, ICU admission, ventilatory required, site of bite, plasma exchange sessions and antivenom dose. Table 2 provides the levels of platelet, PT, INR, and aPTT.

4. Discussion

Plasma exchange has been used in the treatment of more than 70 different diseases. Recently, the clinical applications of plasma exchange are increasing, particularly as a method of detoxification in poison and drug cases [1,5,11]. Plasma exchange is an alternative technique for the removal of protein-bound toxins that are not readily removed with dialysis or hemoperfusion. Plasma exchange is effective in removing highly protein-bound toxins from the blood but not from other fluid compartments [5,11]. Toxins in snake venom connect to many different proteins in the hemostatic system. Therefore, plasma exchange may be of benefit in eliminating venom toxins in the blood compartment and may even result in the redistribution and elimination of venom toxin from the extravascular space.

The first case of plasma exchange used to treat snake bite envenomation was reported by Kornalik in 1990 [12]. In 1994, Rasulov and Berdymuradov reported the application of plasma exchange in the treatment of three of 24 patients with snake bite envenomation. In these patients, fresh frozen plasma was used as replacement fluids, and 2–3 sessions of plasma exchange were performed [13]. In the literature, other successful applications of plasma exchange in cases of snake bite victims were reported. These reports support the efficacy of plasma exchange for treatment of snake bite envenomations, especially in patients with coagulopathy [5,14–18]. These reports indicated clear benefit from plasma exchange, similar to the findings from our study. Other studies showed partial benefits [19,20]. Although we had no control group, we believe that early application of plasma exchange can reduce hospital stays, minimize complications, and decrease the risk of limb amputation as a result of snake bites.

Snake venom can lead to systemic symptoms, such as gastrointestinal, neurologic, renal, and cardiovascular symptoms. Clinical signs may include swelling, ecchymosis, dizziness, vomiting, hypotension, weakness, lethargy, paralysis, ataxia, arrhythmias (e.g., ventricular tachycardia, ventricular premature contractions, ventricular fibrillation), bleeding, diplopia, visual defects, and airway problems such as difficulty in swallowing and opening of the mouth [5,7,8,21]. One patient in our series developed visual problems, which resolved after plasma exchange.

Monovalent horse antivenom is generally used to treat snake bites in Turkey, but the antivenom available in Turkey does not contain antibodies for all Turkish snakes. Antivenom serum cannot be specific in cases where the snake type is not known. Therefore, we believe that the patients who did not recover with antivenom and aggressive supportive care might not have received specific antivenom.

Toxins in snake venom influence the hemostatic system at many different points and cause coagulopathy. As a result, many problems may occur [7,10]. Removal of those toxins through the use of antivenom may facilitate a return to normal homeostasis. Of course, antivenom cannot repair injuries due to coagulopathy, nor can it eliminate all toxins entirely. Moreover, if the type of snake is not known, antivenom therapy may not be effective. However, it is important to administer the correct antivenom as early as

Fig. 1. Examples of snake bite victims. (A) Subcutaneous hematoma on the upper extremity. (B) Subcutaneous hematoma on the lower extremity.

Table 1
Demographic and clinical characteristics of snake bite patients.*

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
Age	59	49	54	52	60	34	35	45	26	52	57	16	53	79	20	31	27	48	43	23	56	21	53	50	34	17	70	28	13	25	16	72	60	66	61	41	75
Gender	M	M	M	M	M	M	M	M	M	M	M	F	F	F	M	F	F	M	M	F	M	F	F	F	M	M	M	M	F	F	M	F	F	M	F	F	F
Hospital stay (days)	8	7	6	11	8	7	4	8	5	9	11	17	6	7	8	10	8	9	21	7	9	14	13	20	14	27	14	12	28	13	21	10	10	25	18	10	18
Site of bleeding																																					
Subcutaneous	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosal		+			+						+	+				+	+		+		+								+								
Gingival					+						+					+	+		+		+								+								
Tracheal																			+		+								+								
Nasal					+							+							+		+								+								
ICU admission												+				+			+							+	+		+		+			+			
Ventilatory required																			+										+								
Site of bite																																					
Upper extremity	+	+	+		+				+	+	+		+	+	+		+	+		+		+	+	+	+		+							+			
Lower extremity				+		+	+	+				+				+			+		+					+		+		+	+		+		+	+	+
Head and neck																													+								
Plasma exchange sessions	3	2	1	1	4	2	2	2	2	1	3	3	2	2	2	3	4	2	3	1	3	1	1	3	1	4	1	1	4	1	3	1	1	3	2	1	2
Dose of antivenom	7	6	4	5	9	6	6	7	6	5	7	7	5	6	7	6	8	6	8	6	6	?	5	8	5	6	?	5	10	6	8	6	5	7	6	5	6

* F, female; M, male.

Table 2
Hematologic parameters in snake bite patients before and after plasma exchange.

	Before plasma exchange	After plasma exchange	*P*
Platelet ($\times 10^3$ µl)	86.25 ± 57.17	241.87 ± 61.09	<0.01
PT (s)	18.15 ± 1.8	12.50 ± 1.2	<0.01
INR	1.47 ± 0.2	1.05 ± 0.1	<0.01
aPTT (s)	27.6 ± 3.1	28.2 ± 2.9	>0.01

possible. In this regard, plasma exchange should be considered as a complementary treatment method for patients with severe snake bite envenomation, especially in the management of hematologic problems and in limb preservation/salvage strategies. Some studies support the efficacy of plasma exchange in the treatment of snake bite envenomation [5,12–18]. In our study, laboratory and clinic improvement was provided with plasma exchange therapy in patients whose hematologic parameters and clinical condition did not improve with antivenom and aggressive supportive care. This result supports the usefulness of plasma exchange therapy. In this context, we think that plasma exchange therapy has beneficial effects by eliminating toxins and inflammatory mediators.

In summary, as was determined from our experience, plasma exchange may be effective in limb salvage strategies and management of hematologic problems in snake bite envenomation victims who do not improve despite aggressive supportive care and antivenom therapy. Extensive randomized controlled trials should be performed to clarify the efficiency of plasma exchange in snake bite envenomation. Plasma exchange may be considered as part of the treatment for snake bite envenomation that cannot be successfully treated with conventional methods.

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