



The effect of plasmapheresis therapy on management of patients with snakebite

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Abstract

Aim: The aim of the study was to evaluate the effectiveness of plasmapheresis therapy in patients with snakebite who were admitted to intensive care unit in the setting of tertiary referral hospital.

Materials and Methods: The retrospective study involved 114 adult patients with snakebite who were admitted to a referral hospital's intensive care unit between January 2012 and December 2022. The patients were divided into four groups according to the treatments. Group AV performed antivenom (Group AV) alone. Group PP performed plasmapheresis alone. Group AV+PP performed antivenom and plasmapheresis. Group GST performed only general supportive therapy.

Results: Fifty two of 114 were included in Group GST, 31 in Group AV, 18 in Group PP and 13 in Group AV+PP. APACHE score, SOFA score, GCS, stage of the bite, length of stay in the intensive care unit, acute kidney injury, and hematological disorders were higher while the platelet count at admission was lower in Group PP and Group AV+PP compared to Group AV and Group GST ($p < 0.05$).

Conclusion: Antivenom and plasmapheresis are not alternatives to each other, antivenom should be performed to patients according to the severity of the bite, and plasmapheresis should be performed without delay in those with severe hematological effects.



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Introduction

An estimated 1.2–5.5 million people are affected by snakebites worldwide each year, with 94,000 of them resulting in death. The country where snakebites and snakebite-related deaths are highest is India [1,2]. This is associated with relatively poor living conditions, high prevalence of venomous snakes, poor access to healthcare, and performing insufficient amount of antidote [3]. Snake venom can be hemotoxic, neurotoxic, myotoxic, nephrotoxic or mixed. Hemotoxic snakebites constitute an important group that causes morbidity and mortality [4]. Ten species of the venomous snakes determined to live in our country belong to Viperidae, two species belong to Colubridae, and one species belongs to Elapidae family. *Viperidea aspis* snakes are mostly found in the area we serve, and most of our patients have hematotoxic ef-

fects [5]. Snake antivenom, which neutralizes circulating venom components, is the only specific treatment for these patients [6]. However, it is not always possible to reach the sufficient amount of antivenom. Therefore, antivenom alone may not be sufficient in patients with systemic effects and who perform to health institutions late, and additional treatment methods such as plasmapheresis, renal replacement therapy or surgery may be required depending on the type of systemic involvement.

The aim of the study was to evaluate the effectiveness of plasmapheresis therapy in patients with snakebite who were admitted to intensive care unit in the setting of tertiary referral hospital.

Materials and Methods

The study was designed as a retrospective observational cohort study in the anesthesiology and reanimation intensive care unit (ICU) of university hospital between January 2012 and December 2022. The university's Institutional

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Review Board approved the study design (Inonu University Health Sciences Non-invasive Clinical Research Ethics Committee, 2022/3470).

Patients' medical records were reviewed and analyzed retrospectively. A total 162 patients were treated in ICU for snakebite. Of 162 patients, 114 were included in this study whereas 48 were not included in the study because of missing data. In our clinic, snakebites are graded and managed according to WHO recommendations [7]. Sometimes, it is not possible to reach enough antivenom for various reasons. Therefore, patients with snakebite may require additional treatments. Patients were divided into four groups according to the treatment they received: those who received general supportive treatment only (general supportive treatment, Group GST), those who received snake antivenom (Group AV) alone, those who performed plasmapheresis (Group PP) alone, and those who performed plasmapheresis with snake antivenom (Group AV + PP).

When there is no antivenom, plasmapheresis was performed to the treatment in cases of rapid decrease in platelet count (platelet counts less than 100.000), increase in LDH, presence of schistocyte in the peripheral smear, or fragmentation above 2-3%. Also, plasmapheresis was performed to patients whose platelet count continued to decrease, still increased LDH level and presence of schistocyte in the peripheral smear, or fragmentation above 2-3% despite of antivenom therapy. Additionally, blood and blood products are also used to the treatment in emergency situation.

Age, gender, APACHE score, location and degree of bite, hematological and neurological involvement, acute kidney injury, development of compartment syndrome and additional treatments of the patients were recorded on standard data sheets. In addition, the Sequential Organ Failure Assessment (SOFA) Score, Glasgow Coma Score (GCS), blood urine nitrogen (BUN), creatinine, platelet, leukocyte, hematocrit, lactic dehydrogenase, aPTT, INR, fibrinogen and D-dimer in the first 24 hours after admission to the intensive care unit were recorded.

Snakebite degree: Stage 0: No local or systemic findings at the first 8-12 hours, stage 1: minimal edema around bite without systemic findings, stage 3: edema not exceeding half of the affected extremity, ecchymosis, minimal hematologic abnormalities, edema in the whole extremity, serious pain, compartment syndrome, and serious systemic findings (for example, shock, loss of muscle strength, coagulopathy, spontaneous bleeding, acute renal failure) [7,8].

Statistical analysis

IBM SPSS Statistics (v22.0; SPSS Inc. Chicago IL, USA) program was used for statistical analysis in the study. The suitability of the parameters to the normal distribution was evaluated with the Levene test. While evaluating the study data, quantitative data were compared as well as descriptive statistical methods. Scheffe test was used for the comparison of normally distributed parameters between groups, and Tamhane test was used for the comparisons of non-normally distributed parameters. Chi-square test and Fisher's Exact Chi-square test were used to compare

qualitative data. Mann Whitney U test and Kruskal Wallis test were used to compare non-parametric data between groups. Significance was evaluated at the $p < 0.05$ level.

Results

The records of 114 patients followed up with snakebite in ICU were obtained. Of the 114 patients, 70% of were male and 30% were female in our study. 52 out of 114 were included in Group GST, 31 patients were in Group AV, 18 patients were in Group PP and 13 patients were in Group AV+PP. There was no significant difference between the groups in terms of age and gender.

Table 1 lists patients' characteristics and other case details of the patients according to treatment groups during ICU admission. The APACHE score was higher in Group PP compared to Group GST and Group AV ($p < 0.01$). The SOFA score was higher during admission to the ICU in Group PP and Group AV+PP compared to Group AV and Group GST ($p < 0.001$). The stage of the bite was significantly higher in Group AV, Group PP, and Group AV+PP compared to Group GST ($p < 0.05$, $p < 0.05$, $p < 0.001$, respectively). The stage of the bite was higher in Group PP and Group AV+PP compared to Group AV ($p < 0.05$ and $p < 0.01$, respectively). The length of stay in the intensive care unit was longer in Group PP and Group AV+PP compared to Group AV and Group GST ($p < 0.001$).

Neurological involvement was common in Group AV+PP compared to Group GST ($p < 0.05$) and Group AV ($p < 0.01$). The GCS score at admission to the intensive care unit was lower in Group AV+PP compared to Group GST ($p < 0.01$), Group AV ($p < 0.05$). GCS score at admission ICU was lower in Group GST than Group AV ($P < 0.05$).

Hematological involvement was common in Group PP and Group AV+PP compared to Group GST and Group AV. Acute kidney injury was common in Group PP compared to Group GST and Group AV ($p < 0.05$). Only one patient required renal replacement therapy. Compartment syndrome development was common in Group PP and Group AV+PP compared to Group GST ($p < 0.05$ and $p < 0.001$, respectively). Compartment syndrome development was common in Group AV+PP compared to Group AV. Two of them underwent fasciotomy and one underwent below-knee amputation.

Table 2 showed laboratory findings of the patients according to treatment groups during ICU admission. Platelet count during admission to the ICU was lower in Group PP and Group AV+PP compared to Group AV and Group GST ($p < 0.001$). Hematocrit, WBC and LDH levels did not differ between the groups in both periods. The INR level at admission to the ICU was higher in Group AV+PP compared to Group GST ($p < 0.05$). There were no significant differences among the groups in terms of aPTT, D-dimer, and fibrinogen levels. Blood urea nitrogen and creatinine levels were not significant differences among groups.

Only one patient were died who was performed AV+PP. This patient was 79 years old, and severe hematologic disorders were observed during ICU admission.

Table 1. Patients' characteristics and other case details of the patients according to treatment groups during ICU admission.

	Group GST	Group AV	Group PP	Group AV+PP
Age (year)	48.13±17.60	47.29±18.96	47.66±17.48	51.53±17.48
Gender (M/F)	34/18	22/9	14/4	9/4
Length of stay in ICU (day)	3.50±1.74	4.38±2.67	8.50±3.45*	7.46±2.70*
APACHE score	5.59±4.29	4.93±2.36	8.33±3.82*	8.38±5.53*
	4 (0-19)	5 (0-9)	8 (2-15)	6 (2-20)
SOFA	1.48±1.61	1.31±1.09	3.61±1.97	6.00±3.13
	1 (0-6)	1 (0-4)	3 (0-7)	5 (2-12)
GCS	14.73±0.59	14.84±0.57	14.44±0.98	13.33±2.34
	15 (8-15)	15 (12-15)	15 (12-15)	15 (8-15)
Degree of bite				
0°	13 (25)	2 (6.5)	1 (5.6)	0 (0)
1°	32 (61.5)	21 (67.7)	4 (22.2)	2 (15.4)
2°	6 (11.5)	4 (12.9)	9 (50)	8 (61.5)
3°	1 (1.9)	4 (12.9)	4 (22.2)	3 (23.1)
Bitten area				
Upper extremity	32 (61.5)	18 (58.1)	8 (44.4)	2 (15.4)
Lower extremity	19 (36.5)	12(38.7)	10 (55.6)	10 (76.9)
Head	0 (0)	1 (3.2)	0 (0)	1 (7.7)
Compartment syndrome	1 (2)	1 (3.2)	3 (16.7)	4 (30.8)
Hematological effects	7 (13.5)	4 (12.9)	14 (77.8)	12 (100)
Neurological effects	6 (11.5)	1 (3.2)	3 (16.7)	5 (38.5)
Acute kidney injury	3 (5.8)	1 (3.2)	4 (22.2)	2 (15.4)

APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale.

Table 2. Laboratory findings of the patients according to treatment groups during ICU admission.

	Group GST	Group AV	Group PP	Group AV+PP
BUN (mg/dl)	15.98±5.29	15.03±4.65	23.87±11.58	20.33±8.39
Creatinine (mg/dl)	0.82±0.21	0.78±0.18	0.98±0.41	1.07±0.51
Platelet (10 ³ /ul)	204.90±80.47	214.68±67.14	86.55±78.41	69.58±43.84
LDH (U/L)	292.88±131.02	288.19±103.57	318.66±119.06	333.77±97.47
Leukocyte (10 ³ /ul)	11.83±4.34	17.05±19.70	17.33±4.90	15.05±5.39
Hematocrit (%)	41.70±6.96	42.63±6.15	45.03±9.50	39.98±11.39
aPTT (s)	27.26±6.84	32.30±19.96	29.26±15.71	33.51±17.95
INR	1.01±0.98	1.17±0.51	1.13±0.18	1.33±0.36
D-dimer (mg/L)	5.82±14.21	3.53±3.48	5.48±6.35	4.865±6.52
Fibrinogen (mg/dl)	208.50±100.38	180.98±117.48	169.50±40.93	116.91±100.56

BUN: blood urea nitrogen, LDH: lactate dehydrogenase, INR: international normalized ratio.

Discussion

Our university hospital is the referral hospital for the region, and a part of snakebites are also followed and treated in our tertiary intensive care unit. In our clinic and hospital, follow-up and treatment are carried out according to the recommendations of WHO [7,8]. A patient population over a period of approximately 10 years was screened retrospectively in our study.

The use of antivenom is the only treatment method that will prevent systemic effects and progressive tissue damage by directly neutralizing the venom in snakebites [6]. There are many types of antivenom, mono- or polyvalent, those are effective against one or more snake venoms in the world [9]. Polyvalent antivenom (containing at least

500 LD50 *Macroviperia lebetira*, 500 LD50 *Montiviperia xanthina*, and 1000 LD50 *Vipera ammodytes* snake venoms of equine-derived antitoxic immunoglobulin fragments in each 10 ml) is performed in our country and therefore in our hospital. However, both the delay in the transfer of patients from rural or low-level health institutions to our hospital and the inability to obtain a sufficient amount of antivenom in our clinical practice and the inability to apply it in the early period may result in the insufficient use of antivenom and worsen the clinical outcome of the patient. Therefore, when antivenom cannot be performed because of absence for various reason or used insufficient amounts for its stage, progressive tissue damage develops and toxicity progresses and hemolysis, thrombocytopenia, bilirubinemia, acute kidney injury may occur.

In this case, according to the clinical presentation, other treatment methods such as transfusion of blood and blood products, plasmapheresis, renal replacement therapies and fasciotomy are used. Although plasmapheresis is life-saving in patients with hematological disorders, it is a limited resource that is not available in every center, has high cost and has its own side effects. Renal replacement therapy can be used in patients with acute kidney injury who do not respond to medical treatment.

In our study, we divided the patients into 4 groups according to the treatment. It was observed that in 31 of the patients, antivenom alone was sufficient in the treatment, 18 patients with hematological disorders but unable to reach antivenom were treated with plasmapheresis until the patient recovered. The remaining 52 patients were followed up due to progressive local tissue damage and mild systemic involvement, and no additional treatment was performed except for blood and blood product transfusion and general supportive treatment. Of the 114 patients, 70% of were male and 30% were female in our study. In the literature, it was reported that 59% of snakebites were men and 28% were children [3]. Since pediatric patients were not followed up in our intensive care unit, we do not have information about the number of pediatric cases, but the other rates of our study were consistent with the literature.

The patients with the worst APACHE score, SOFA and GCS score in other words, the most severe patients were in Group AV+PP, followed by Group PP. This situation might be related to the severity of the bite stage in ICU admission, because the stage of the bite was higher in Group AV+PP and Group PP compared to other groups. As a result, the stage of the bite indicates the severity of the toxicity, and the amount of antivenom used to increase when the severity increases. At the same time, extended length of stay in the ICU, low platelet count, and prolongation of INR in this groups support this opinion.

The low platelet levels in Group PP and Group AV+PP during admission to the ICU are not related to the outcome of the treatment. This can be explained by the addition of plasmapheresis to the treatment in patients with thrombocyte counts below 100.000, with schistocyte or fragmentation above 2-3% in the peripheral smear in our clinic. Plasmapheresis is a blood purification method applied to remove proinflammatory substances, immunoglobulins, or toxins that are involved in the pathogenesis of some diseases from the systemic circulation. As stated in the literature, plasmapheresis is a treatment method that can be used in snakebites with hematological involvement [10,11]. Plasmapheresis is not present in all centers, and it may cause shock, persistent arrhythmia, pulmonary embolism, severe hemolysis, transfusion-related lung injury, heparin-induced thrombocytopenia, and catheter-related complications [12,13]. Immediate presentations of plasmapheresis can be lifesaving when adequate antivenom cannot be obtained or if hematological disorders persist despite sufficient antivenom administration. However, in practice, sending blood samples to the laboratory to demonstrate hematological disorders, consulting for abnormal results, placement of central venous catheter, and preparation for plasmapheresis take time and may result in worsening of

toxic effects. In this case, sudden decrease in platelets requires transfusion of blood and blood products, according to the clinic, in hematologic disorders occurring in the period until plasmapheresis. The high INR in Group AV+PP is due to the fact that it is the group with the highest hematological disorders.

Neurotoxicity varies depending on the type of snake and thus the antivenom, and geographical location. Presynaptic and post-synaptic areas of the neuromuscular junction may be affected. It may occur in the early and late periods [14,15]. Descending paralysis is characteristic. Clinical presentation can range from ptosis, respiratory failure, hypoxic ischemic encephalopathy to cerebral ischemia, infarct, and posterior reversible encephalopathy syndrome [16,17]. We did not detect any serious neurological involvement in our patients. The low Glasgow coma score was thought to be due to systemic effects such as hypotension and emotional factors.

While Aye et al. reported the incidence of acute kidney injury due to snake envenomation as 54.3%, and Tchaou et al. reported that it was 31%, Gopalakrishnan stated that it was under-reported [18-20]. Studies have shown that the incidence of AKI in patients with thrombotic microangiopathy is as high as 94% [21,22]. In our clinic, the diagnosis of AKI is made according to the criteria of KDIGO. In our study, it was found that only 10 of the patients developed AKI, more so in Group PP.

While Hsu et al. reported that compartment syndrome developed 9 out of 136 patients, and Kim et al. reported that approximately 10.8% of the patients in their study needed fasciotomy [23,24]. In our clinic, 9 out of 114 patients developed compartment syndrome; majority of them were in the Group AV+PP.

One of limitations of this study is that it is a retrospective study, but this situation is not available for a randomized controlled study. Other limitations are that includes a single center's experience, and the time between bite and treatment is unknown.

Conclusion

Since snakebites can cause morbidity and mortality, patients with advanced stages or those who are predicted to progress should be followed up in the intensive care unit. In intensive care unit, appropriate antivenom dose should be performed rapidly according to the bite stage. Antivenom and plasmapheresis should not be considered as alternative treatment methods for each other. Patients should be carefully monitored for intravascular hemolysis, acute kidney injury and compartment syndrome in order to use an increasing amount of antivenom in patients with progressive tissue damage and systemic effects, to add plasmapheresis to the treatment without delay in those with severe hematological disorders, and to delay initiating the necessary interventions.

Ethical approval

This study was approved by the Inonu University Health Sciences Non-invasive Clinical Research Ethics Committee (2022/3470).

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