



Original Contribution

The efficacy of low-dose antivenom therapy on morbidity and mortality in snakebite cases

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Abstract

Similar to the cases seen around the world, snakebite causes mortality and morbidity in Turkey. The venom of different types of snake in the region of Çukurova causes serious systemic and local tissue damage.

Methods: We performed this prospective study on 45 patients who complained of snakebite. We grouped the patients according to their clinical presentations to facilitate treatment and follow-up period procedures.

Results: Whereas the patients with grade 1 envenomation did not receive any antivenom, grades 2 and 3 patients received 2.70 ± 0.77 and 4.88 ± 1.65 vials of antivenom, respectively. One of our patients had to undergo finger amputation but there were no deaths. Allergic reactions developed after antivenom therapy in 8 patients (17.8%).

Conclusions: When we considered the cost and complications of the antivenom treatment, it was seen that low-dose antivenom treatment effectively treated the patients with venomous snakebite injuries in our region.

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1. Introduction

Similar to the cases seen around the world, snakebite causes mortality and morbidity in Turkey. Venomous snakes such as *Vipera ammodytes meridionalis* and *Vipera lebetina obtusa* can often be found in the region of Çukurova. The venoms of these snakes may cause not only sudden death by activating the coagulation system which causes disseminated intravascular coagulation, but also loss of limb by the effect of tissue necrosis [1,2].

Antivenom is the suspension of various antibodies obtained from horse serums which are hyperimmunized against snake venoms. Although mortality rates were 5% to 25% before the use of snake antivenom, they decreased to 1% and to 0.1% in well-treated patients after the use of snake antivenom [3–5], but there are still different views as to the use of antivenom. Whereas researchers who advocate the use of antivenom therapy claim that the use of the antivenom could return some systemic and local tissue damages of the snake venom, researchers with opposing views assert that the antivenom produces serious allergic reactions and that, scientifically, there is no evidence showing a change in morbidity and mortality rates [3,6]. Therefore, many authors

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Table 1 Clinical presentation and treatment according to grade of envenomation [3]

Grade of envenomation	Clinical presentation	Antivenin treatment	Other treatment	Follow-up
No envenomation (grade 0)	No evidence local and systemic envenomation	Not use	Wound care, tetanus toxoid, prophylactic antibiotic (?)	Observe for 12 hours
Minimal envenomation (grade 1)	Minimal local tissue swelling, no systemic envenomation, normal laboratory finding and no progression	Not use	Wound care, tetanus toxoid, prophylactic antibiotic (?)	Observed for 12 h
Moderate envenomation (grade 2)	Progressing local tissue swelling, local pain, and ecchymoses. Minimal systemic envenomation and laboratory finding	4-10 antivenin vials	Tetanus toxoid, broad-spectrum antibiotic, monitoring vital functions, intravenous fluids, pain treatment, fasciotomy in intracompartmental syndrome	Considered for intensive care unit admission
Severe envenomation (grade 3)	Progressive swelling, pain, ecchymoses, hemorrhage, necrosis. Systemic symptoms, coagulopathy, cardiopulmonary arrest, acute renal failure	10-40 antivenin vials	Tetanus toxoid, broad-spectrum antibiotic, monitoring vital functions, intravenous fluids, pain treatment, fasciotomy in intracompartmental syndrome	Observed in the intensive care unit

suggest different antivenom doses for venomous snakebites recently [7-13].

The purpose this study was to investigate what kind of envenomation clinic occurs via snakebites in the region of Çukurova and to investigate the efficacy of low-dose antivenom therapy in the recovery of systemic envenomation and local tissue damage signs compared to high-dose antivenom therapy with respect to its complications and costs.

2. Methods

Forty-five consecutive patients admitted to the Çukurova University Faculty of Medicine Hospital Emergency Department with the complaint of snakebite between June 2000 and August 2003 participated in the study.

Inclusion criteria to the study were as follows:

1. Definite teeth traces at the bite site; the two holes which are half inch apart from each other where swelling, pain, and color change occur.
2. In case of depredation of the teeth traces because of multiple cut applications, the patients must have seen the snake and must have clinical symptoms compatible with the venomous snakebite.
3. Willingness of the patients to participate in the study.

Exclusion criteria from the study were as follows:

1. Absence of teeth trace.
2. Presence of a known disease of the patient which can lead to a bleeding disorder.
3. Use of a drug which can lead to a bleeding disorder.

While determining clinical staging, initial vital signs (blood pressure, pulse rate, number of respiration), local tissue signs, presence of systemic signs, and laboratory data were used [4,6]. The clinical staging system that we used in the management of snakebite cases is shown in Table 1. According to this system, the stages of the patients (those admitted to the ED with the complaint of snakebite and had the inclusion criteria) were identified. Patients who were identified to be stage 0 and had no visible snake teeth trace were excluded from the study. These patients were kept in the ED in terms of tissue edema and systemic findings for 12 hours. At the end of 12 hours, patients without tissue edema at the site of the bitten region and patients with no systemic findings were discharged from the hospital. During their hospital stays, all patients were monitored for their vital signs and checked for urine outputs per hour and proper fluid replacement was applied. Also, pain relief was remedied only by paracetamol when required. Antivenom-treated patients were followed at the intensive care unit. The vital signs of patients having an initial hypotension (<90/60 mm Hg), tachycardia, and tachypnea were stabilized. To detect the increase in edema, initial edema borders were marked and progression of the edema was followed. The bitten extremity of the patient was followed with immobilization and checked for compartment syndrome carefully. Presence of systemic bleeding signs (petechia, gingival bleeding, nose bleeding, hematuria, gastrointestinal system bleeding, etc) was assessed, and initial coagulation tests (thrombocytopenia, hypofibrinogenemia, the increase of fibrin destruction products, PTZ, and activated partial thromboplastin time [APTT] from the aspect of growing) were checked and repeated every 4 to 6 hours. The patients who had hematological thrift diagnosis consulted with the Department of Hematology. In the progressive period, fresh frozen plasma was applied to treat hematological disorders. Antivenom



Fig. 1 Grade 3 envenomation with snakebite patient local tissue finding.

treatment was also discontinued in the patients who developed acute allergic reaction during antivenom application.

Antivenom was not applied to the patients who were accepted to be stage 1 and showing no clinical deterioration during their hospital stays. Approximately 2 to 4 vials and 4 to 8 vials 1/10 time of diluted (by serum physiologic solution) antivenom were applied to moderate-envenomation (stage 2) and severe-envenomation (stage 3) patients, respectively (Figs. 1 and 2). Fresh frozen plasma was applied to the patients who had consumption coagulopathy in their follow-ups. Fresh blood or concentrated erythrocytes were transfused to the patients as far as possible who became anemic during their hospitalization. All patients were informed about the study, and a consent form was obtained. The study was approved by the local ethics committee.

2.1. Laboratory

White blood cell (WBC), hemoglobin, hematocrit, and platelet counts were evaluated by CBC Coulter Technique using Coulter STKS and Coulter Gen-S machine. Biochem-



Fig. 2 Grade 3 envenomation with snakebite patient severe tissue swelling (up to the trunk and axilla).

ical parameters (glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, creatinine phosphokinase, alanin aminotransferase, aspartate aminotransferase) were evaluated by enzymatic calorimetric test using the Integrated Cobas 800 biochemical analyzer. Serum electrolytes (sodium, potassium, and chloride) were measured by ion-selective electrode method, and bilirubin measurements (total bilirubin, indirect, and direct bilirubin) were applied by spectrophotometric method and with diazo reaction. Prothrombin time, APTT, fibrinogen, and fibrin destruction products were analyzed using the Organon Technica device.

2.2. Statistical analysis

SPSS for Windows version 13.0 (SPSS, Inc, Chicago, Ill) was used for statistical analysis. The Student *t* test was used to analyze parametric variables. A *P* value of .05 or less was considered statistically significant.

3. Findings

Forty-five patients were accepted into the study. Twenty (44.4%) of them were female and 25 (55.6%) were male. Their average age was found to be 40.3 ± 18.8 years. Thirteen (28.9%) patients had a known systemic disease history. A female patient aged 25 years was 20 weeks pregnant. The baseline clinical characteristics of the study group are shown in Table 2.

The average time for hospitalization after snakebite was found to be 10.1 ± 13.9 (1-72) hours. The bite places of all patients were in their extremities. Twenty-eight (62.2%) of them were bitten on their feet, 5 on their arms, and 12 on their fingers. The number of stage 1, stage 2, and stage 3 patients who went to our ED with the complaint of snakebite was 11 (24.4%), 17 (37.8%), and 17 (37.8%), respectively.

Thirty-eight (84%) patients were detected to have leucocytosis (≥ 9000 per cubic millimeter of leucocytes were accepted to be leucocytosis). Their peripheral blood smear examinations were found to be compatible with leucocytosis. Polymorph nucleated leucocytes were found to be predominant in their peripheral blood smears. The mean

Table 2 Baseline clinical characteristics

	Average $\pm$ SD (DL-UL)
Age (y)	40.3 $\pm$ 18.8 (9-75)
Sex (female/male)	20/25
Systolic blood pressure (mm Hg)	113.5 $\pm$ 24.8 (60-180)
Diastolic blood pressure (mm Hg)	73.0 $\pm$ 17.6 (30-110)
Pulse (/min)	92.0 $\pm$ 16.3 (60-136)
Breathing number (/min)	20.3 $\pm$ 3.5 (14-30)
Pregnancy	1
Exitus	0

DL indicates down limit; UL, up limit.

Table 3 Relation of systemic envenomation grade and laboratory parameters

	Grade 1	Grade 2	Grade 3	P (1-2)	P (2-3)	P (1-3)
WBC (10^3)	11.1 $\pm$ 3.6	13.6 $\pm$ 4.7	16.5 $\pm$ 4.9	0.121	0.096	0.003
Hemoglobin	13.0 $\pm$ 1.5	13.5 $\pm$ 1.8	12.8 $\pm$ 2.9	0.384	0.385	0.852
Hematocrit	38.5 $\pm$ 4.1	40.5 $\pm$ 4.3	37.5 $\pm$ 9.4	0.224	0.234	0.699
Platelet (10^6)	251 $\pm$ 67	138 $\pm$ 44	56 $\pm$ 29	0.000	0.000	0.000
PTZ	13.9 $\pm$ 1.4	14.4 $\pm$ 2.0	25.2 $\pm$ 27.3	0.426	0.015	0.016
APTT	28.2 $\pm$ 3.9	29.7 $\pm$ 6.5	62.4 $\pm$ 61.7	0.464	0.037	0.037
Fibrinogen	338 $\pm$ 179	321 $\pm$ 143	230 $\pm$ 122	0.795	0.055	0.099
Glucose	170 $\pm$ 118	133 $\pm$ 38	189 $\pm$ 127	0.332	0.095	0.703
BUN	15.5 $\pm$ 4.4	17.4 $\pm$ 4.9	23.7 $\pm$ 14.6	0.321	0.092	0.039
Creatinine	0.76 $\pm$ 0.16	1.01 $\pm$ 0.55	1.00 $\pm$ 0.50	0.096	0.948	0.084
SGOT	30.5 $\pm$ 10.2	27.2 $\pm$ 9.1	38.8 $\pm$ 25.1	0.390	0.084	0.236
SGPT	20.1 $\pm$ 9.6	19.9 $\pm$ 4.5	29.4 $\pm$ 18.4	0.947	0.046	0.091
LDH	540 $\pm$ 221	508 $\pm$ 166	585 $\pm$ 402	0.686	0.467	0.702
Amylase	48.4 $\pm$ 13.0	44.6 $\pm$ 17.1	42.2 $\pm$ 16.9	0.521	0.682	0.291
Na	139 $\pm$ 5	140 $\pm$ 3	138 $\pm$ 4	0.482	0.048	0.498
K	4.2 $\pm$ 0.3	4.1 $\pm$ 0.5	4.4 $\pm$ 0.5	0.443	0.130	0.332
Cl	100 $\pm$ 5	102 $\pm$ 3	103 $\pm$ 4	0.552	0.285	0.104
CK	94 $\pm$ 69	148 $\pm$ 183	225 $\pm$ 133	0.285	0.166	0.002
CK-MB	2.65 $\pm$ 0.67	2.91 $\pm$ 1.51	4.24 $\pm$ 1.45	0.542	0.013	0.001
Troponin T	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	1.000	1.000	1.000

BUN indicates blood urea nitrogen; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; LDH, L-lactate dehydrogenase.

WBC number of the patients was found to be 14077.33 ± 4933.76 (6000-27000) mm^3 and a positive correlation was found between WBC number and systemic stage of the patients ($P < .05$). Complete blood counts, total biochemistries, and the relation between the coagulation parameters and systemic stages before treatment are presented in Table 3.

Only 7 (15.6%) patients had findings of bleeding diathesis (gingival bleeding, nose bleeding, petechia, etc) during their hospitalization. Hemoglobin and hematocrit levels of 4 (8.9%) patients who had severe tissue edema, diffuse echymotic regions, and signs and symptoms related to bleeding diathesis were less than 19 g/dL and less than 30%, respectively. Fresh blood was given to these patients as far as possible. In the absence of fresh blood, fresh frozen plasma or concentrated erythrocyte suspension was given.

The mean thrombocyte score of the patients was found to be 134655 ± 88040 (10500-350000) U/L. The thrombocyte level of 30 (66.7%) patients was found to be lower than 150000 (10500-149000) U/L. Seven (15.6%) patients had a PT longer than 18 seconds and an APTT longer than 45 seconds. These 7 patients also had low fibrinogen levels.

Five patients had clinical deterioration during their hospitalization.

3.1. Case 1

Stage 1 envenomation findings progressed to stage 3 during his hospitalization. Six antivenom vials were applied to the patients who were not given any initial antivenom during hospital admission.

3.2. Case 2

It was planned to give 2 antivenom vials to the patient who had been hospitalized for being at stage 2. Antivenom treatment was stopped immediately with the patients who developed anaphylaxis during antivenom application. Treatment for anaphylaxis was started. Stage 2 envenomation findings progressed to stage 3 during his hospital stay.

3.3. Case 3

Two antivenom vials were given to the patient who was hospitalized with stage 2 envenomation findings. Stage 2 envenomation findings progressed to stage 3 during his hospital stay. Then, 4 more antivenom vials were given to the patient.

3.4. Cases 4 and 5

Two patients with stage 1 envenomation progressed to stage 2. Two antivenom vials were given to both patients.

Another case was a stage 2 woman with 20 weeks of gestation. Four antivenom vials were applied. During her follow-up at the hospital, she had no problem and completed her pregnancy and she gave birth to a healthy baby.

A total of 129 snake antivenom vials for 34 (75.6%) patients were used in our study. No antivenom was applied to stage 1 patients, but 2.70 ± 0.77 antivenom vials to stage 2 and 4.88 ± 1.65 antivenom vials to stage 3 patients were applied. Despite our use of low-dose antivenom treatment,



Fig. 3 Snake which was killed by snakebite patient and its type was identified as *Vipera lebetina obtusa* by the Department of Biology.

complete recovery was detected in all of our patients. Related to the snake antivenom, acute allergic reaction developed in 7 (15.6%) patients and pyrogenic reaction developed in 1 (2.2%) patient. Urticarial plaques were seen in 3 (6.7%) of 7 patients who had acute allergic reaction and anaphylactic shock findings were seen in the other 4 (8.9%) patients developing allergic reaction. During the follow-up of all patients, no death occurred resulting from either systemic or local effects of snake venoms or allergic reactions against antivenom use.

4. Discussion

There are 40 types of snake in Turkey and the Viperidae snake group is the most frequently seen. In the region of Çukurova, the venomous types such as *Vipera ammodytes meridionalis* and *Vipera lebetina obtusa* are often found. In our study, the snakes that the patients brought were identified in the Department of Biology. These snakes were the same as the ones often seen in our region (Fig. 3).

Snake venom has various effects on the bitten site and on the whole body [2]. It may cause pain, edema clinic at the bitten site, and life-threatening disorders such as bleeding and coagulation disorders, renal failure, and shock [14]. The mortality ratios are kept low by applying an appropriate first aid and an effective treatment. Therefore, the first thing to do at the time of hospital admission is to determine the stage of the disease and ameliorate the abnormal vital signs.

All snakebite patients should be monitored for at least 12 hours at the ED [3,15]. The clinical staging system developed for snakebites by Roberts and Otten [3] makes the management of this group of disease easier. Besides this, antivenom use in snakebites should be determined according to the clinic (stage) of the patient [6]. By using this staging

system, we followed up all the patients undergoing antivenom treatment at the intensive care unit.

Leucocytosis is a very common symptom in snakebites and it is caused by stress and the inflammatory response of the body [3]. The increase in the WBC number is an expected symptom as the clinical stage of the disease increases ($P < .05$). It is known that thrombocytopenia and bleeding diathesis findings are caused by the hemotoxins of the snake venom [6,14,16]. The average thrombocyte score of our patients was found to be low, and also 7 patients had a PT of more than 18 seconds and an APTT of more than 45 seconds. These 7 patients were also found to have low fibrinogen levels. The clinical findings of these patients improved with the antivenom therapy and supportive treatment.

Horse serum skin test is the test being used before the application of snake antivenoms, but it is not contraindicated to use antivenoms to snakebite patients who have a positive skin test. It could also cause acute allergic reactions, even anaphylaxis and death in patients who have a negative skin test [17-19]. Because of this, we did not perform horse serum skin test before the application of antivenoms.

One hundred twenty-nine snake antivenom vials were used in 34 patients in our study. Antivenoms were not applied to stage 1 patients, but 2.70 ± 0.77 antivenom vials to stage 2 and 4.88 ± 1.65 antivenom vials to stage 3 patients were applied. After we used low doses of the antivenoms, being in limited numbers in our stock, we have seen a complete recovery with low-dose antivenom treatment in all of our patients. After hospital discharge, only one patient had finger amputation. Eight (17.8%) patients had acute allergic reaction after antivenom use. Three of them were urticarial rash, 4 were anaphylactic shock, and 1 had pyrogenic reaction.

The proper time and appropriate dose for antivenom application have been controversial for years. Many authors recommend different antivenom doses for venomous snakebites [7-13]. Roberts and Otten [3] did not suggest antivenom use for no-envenomation (stage 0) patients and for patients having mild tissue signs without systemic findings (stage 1). They suggest using 4 to 10 and 10 to 40 vials of antivenom for moderate-envenomation (stage 2) and severe-envenomation (stage 3) patients, respectively. Scharman and Noffsinger [20] evaluated patients in 4 groups and suggested a 0 to 4, 5 to 9, 10 to 15, and 15 or more vial doses of antivenoms to stage 0, stage 1, stage 2, and stage 3 patients, respectively. Juckett and Hancox [14] divided patients into 5 groups and suggested no antivenom use to stage 0 patients (patients with no snakebite), but recommended using 0 to 5, 5 to 15, 15 to 20, and 25 or more antivenom vials for stage 1 (mild envenomation findings), stage 2 (moderate envenomation findings), stage 3 (severe envenomation findings), and stage 4 (life-threatening envenomation) patients, respectively.

Offermen et al [21] conducted a study by using high-dose polyvalent antivenom in 73 snakebite cases admitted to the

ED. They applied 0.7 ± 1.9 , 8.4 ± 4.0 , 11.8 ± 5.7 , and 18.7 ± 6.3 antivenom vials to 7 stage 0, 23 stage 1, 32 stage 2, and 11 stage 3 patients, respectively. They applied 777 antivenom vials for 65 patients. No death was seen. Twelve (18.5%) patients had allergic reactions but all of them responded to the medical treatment. Because of the similar results with Offerman et al (no mortality and frequency of acute allergic reactions was 17.8%-18.5%) in mortality and morbidity aspects, our study suggests that low-dose antivenom treatment in venomous snakebite cases has no significant difference from high-dose antivenom treatment.

Consequently, when we think of the cost and complications of the antivenom treatment, it was seen that low-dose antivenom treatment effectively treated the venomous snakebite cases in our region. We had the feeling that patients who cannot take antivenom treatment because of acute allergic reactions can recover by symptomatic and supportive treatment of vital symptoms and the local and systemic envenomation symptoms, but a wide series of studies are needed further in our region.

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