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Factors Affecting Prognosis in Patients with Snakebite

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Abstract

Aim: This study aimed to determine the factors influencing hospitalization durations and discharge status of patients with snakebite, starting from pre-hospital care in the field.

Materials and Methods: A total of 38 patients with snakebite admitted to the emergency medicine department between May 1st, 2013 and August 31st, 2016, participated in the study. Data were evaluated using Statistical Package for the Social Sciences 17.0.

Results: A total of 38 patients were enrolled, of which, 17 (44.7%) were female. Of the 38 patients enrolled, nine patients were in stage 1, 24 in stage 2, and 5 in stage 3. The mean antivenoms given to patients were 3.33±1.29 vials in stage 2 and 4.40±1.14 vials in stage 3. The mean time from bite to antivenom infusion was 80.92±47.57 mins. Hospitalization durations of patients with shorter bite to antivenom infusion intervals (bite-to-needle) were also shorter ($p<0.001$). In addition, overweight patients were found to stay longer in the hospital ($p=0.027$). Patients with low hemoglobin and platelet counts and high creatine kinase (CK) levels were found to stay longer in the hospital ($p<0.05$).

Conclusion: Shorter hospitalization durations of patients with shorter bite-to-needle times show the importance of early administration of antivenom. Moreover, longer hospitalization durations of overweight patients seem to reflect their slow wound-healing times, which may be due to co-morbidities. Low platelet, hemoglobin, and CK are found to be poor prognostic markers in patients with snakebite.

Keywords: Emergency department, snakebite, prognosis

Introduction

As it is throughout the whole world, snakebite is an important cause of morbidity and mortality in Turkey. The estimated number of snakebite victims is 421,000, resulting in 20,000 deaths worldwide (1). More specifically, the annual number of deaths due to snakebites in India was 1,350 in 2004-2009; in the United States, there are five deaths per 7,000-8,000 bites (2,3). Although serious envenoming occurs with snakebites, proper first aid and efficient treatment may help in reducing mortality.

The species *Macrovipera lebetina* and *Vipera barani* comprise most snakes in our region of Turkey (4). These species' toxins cause serious local tissue toxicity due to consumption coagulopathy. Seasonal variations and the rural nature of this entity cause difficulties for obtaining reliable epidemiological data. For this reason, we aimed to investigate in-hospital factors influencing the hospitalisation durations and discharge statuses of snakebite patients, as well as prehospital factors in the field.

Materials and Methods

Patients who were admitted to the emergency department (ED) of Çukurova University Medical School between July 2013 and August 2016 with a history of snakebite were enrolled in the study. The protocol was approved by Çukurova University Faculty of Medicine Noninvasive Clinical Researches Ethics Committee (decision no: 5, date: 05.07.2013).

The exclusion criteria were receiving anticoagulation treatments, having coagulation problems due to chronic diseases and not having fang wounds.

The patients were monitored in the critical care unit of the ED, where their blood samples were obtained for whole blood count,

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biochemical and coagulation analyses. Clinical staging is used to standardise the diagnosis, treatment strategies and management and determine the severity of the bite in snake bite patients (5). The stages of the envenoming were assessed according to the local and systemic findings. Table 1 reveals the classification of the staging (5).

Primary wound care and prophylaxis for tetanus were given to the patients, and stage 2 and 3 patients received antivenom. The extremities were immobilised, and the interventions and medications given in the previous hospital were recorded. Prophylaxis for wound infection was given if improper first aid had been performed (e.g. cutting and suction of wound or applying herbal ointments). Fresh frozen plasma (FFP) was given at a dose of 10 mL/kg to patients with coagulation abnormalities and non-regressing tissue oedemas after antivenom infusion.

The body mass indices (BMIs) of the patients were calculated. For the BMI, a result <18.5 kg/m^2 is classified as underweight, 18.5-24.9 kg/m^2 as normal weight, 25-29.9 kg/m^2 as overweight, 30-39.9 kg/m^2 as obese and >40 kg/m^2 as highly obese. The patients were assessed repeatedly for antivenom requirements during hospitalisation and given supplemental vials if needed according to the clinical stages.

Statistical Analysis

The data in our study were analysed using SPSS version 17.0. The normally distributed variables were compared using a t-test and repeated measurement analysis. Variables that were not normally distributed were compared using the Mann-Whitney U test and Friedman test. The χ^2 test was used for categorical variables. The results were expressed as the mean (standard deviation), median (minimum-maximum), n and percentage. A p-value less than 0.05 was considered statistically significant.

Results

Thirty-eight patients (44.7% female) were enrolled in the study. Eight (21.1%) had applied independently after snakebite, so our clinic was the first point of medical contact. The other patients were given different treatments in rural hospitals, from which they were transferred to our ED. The demographics and vital signs of the study patients are summarised in Table 2.

Twenty patients (52.6%) were bitten on the lower extremities, 17 (44.7%) were bitten on the upper extremities and one was bitten on the posterior thoracic region. The first systemic staging of the patients was as follows: nine (23.7%) were stage 1, 24 (63.2%) were stage 2 and five (13.2%) were stage 3.

Thirty-five (92.1%) study patients had improper first-aid interventions, such as a tight tourniquet and/or cutting/suction/bleeding in the prehospital field. Three patients had not received any first aid. Thirty (79%) patients who had infection risks due to cutting and suction were started on prophylactic antibiotics, and nine of them had soft tissue infections. Infection was controlled in all the patients.

The mean time interval between bite and antivenom infusion of the study patients was 80.92±47.57 minutes. When the antivenom doses of the patients were examined, stage 2 patients received 3.33±1.29 vials of antivenom, while stage 3 patients received 4.40±1.14 vials. Of the study patients who received additive vials during hospitalisation, the reason was because they received insufficient vials in the previous hospital in 14

Table 1. Clinical staging of snakebite and treatment (5)

Stage	Findings	Antivenom	Supportive care	Hospitalization/discharging
0	No local or systemic findings (first 8-12 hours)	None	Wound care Tetanus prophylaxis	Discharge after observing 8-12 hours if does not progress to stages 1, 2 or 3
1	Minimal edema around bite without systemic findings	None	Wound care Tetanus prophylaxis	24 hours observation with monitorizing
2	Edeme not exceeding half of the affected extremity, ecchymosis, minimal hematologic abnormalities	Needed	Wound care Tetanus prophylaxis İntravenous crystalloids Cardiac monitorization Analgesics Follow-up for laboratory tests	Intensive care unit hospitalization
3	Edema in the whole extremity, serious pain, compartment syndrome, and serious systemic findings (shock, loss of muscle strength, coagulopathy, spontaneous bleeding, acute renal failure i.e.)	Needed	Wound care Tetanus prophylaxis intravenous crystalloids Cardiac monitorization Analgesics Follow-up for laboratory tests Oxygen Vazopressors if needed	Intensive care unit hospitalization

patients and progressive tissue oedema despite proper treatment in four others. Of the 38 study patients, only one experienced allergy due to antivenom, and anaphylactic shock was managed successfully.

The mean hospitalisation durations of the study patients were as follows: 44.22±26.94 hours in stage 1 patients, 54.73±34.32 hours in stage 2 patients and 70.20±9.17 hours in stage 3 patients. The patients with a shorter time interval between the bite and antivenom infusion (bite-to-needle time) were found to be hospitalised for shorter durations (Table 3).

The relationships between hospitalisation durations and patients' BMIs were examined. The study patients were normal or overweight, and the hospitalisation duration was found to be longer in overweight patients (Table 3). The haematological and biochemical analyses of the study patients revealed that low haemoglobin, low platelets and elevated creatinine kinase (CK) are correlated with long hospitalisation durations (Table 4).

Discussion

Snakebite is a serious health problem, especially in tropical regions of the world. Patients can develop long term disability and suffer psychological sequel. The species and poisons vary according to the region, resulting in different clinical findings. The Çukurova region of Turkey is rich with poisonous snakes. *Macrovipera lebetina* and *Vipera barani* are the major poisonous snakes in our region (4). Such species cause local tissue oedema, compartment syndrome, rhabdomyolysis, haemolysis, renal failure and coagulopathy. Local tissue oedema is the major toxicity that occurs after being bitten by our region's snakes, which makes it very important to give proper first aid.

Most feared local complication is compartment syndrome. This situation can lead to permanent disability. However, snakebite patients receiving effective treatment in early period may experience compartment syndrome rarely. The use of tourniquets, which compromise arterial and venous circulation, causes serious oedema and compartment syndrome. In addition to tourniquet use, cutting and suction which were performed by the bystanders also causes damage, and this approach is also still performed in snakebites.

Thirty-eight patients in our study had improper first-aid interventions, while three patients had not received any first aid at all. Nine patients had soft tissue infections despite being started on antibiotics because of cutting and suction of their wounds. All the patients were successfully cured with antibiotics. Delayed treatment in snake bites may cause severe local and systemic serious complications such as necrotizing faciitis and

Table 2. Clinical findings of patients

	Mean ± SD	Min-max
Age	41.7±17.2	18-84
Weight	71.55±12.44	50-90
Height	167.23±7.03	150-180
BMI	25.52±3.84	19-34
Systolic blood pressure	118.94±14.10	70-140
Diastolic blood pressure	72.76±9.20	40-80
Pulse rate	78.86±9.82	61-105
Oxygen saturation	97.57±1.48	94-100
Body temperature	36.52±0.50	35-38

BMI: Body mass index, SD: Standard deviation, min: Minimum, max: Maximum

Table 3. Relation between bite-to-needle time and BMI with hospitalization time

	Hospitalization time	p-value
Bite-to-needle time (minute) 80.92±47.57	(2.25±1.28) (days) (54.0±30.72) (hours)	<0.001
BMI		
Normal weight (n=18)	42.61±26.31 (hours)	0.027
Over weight (n=20)	64.35±31.77 (hours)	

BMI: Body mass index, n: Number

Table 4. Relationship of hospitalization durations and laboratory results

Laboratory results		Hospitalization (Mean ± SD)	p-value
Hb (11.6-15.5 g/dL)	normal	65.20±34.47	0.017*
	low	41.66±21.13	
PLT (156-372 10^3/µL)	normal	74.90±35.10	0.037*
	low	46.60±26.13	
Glucose (70-100 mg/dL)	normal	50.75±23.56	0.617
	high	55.57±34.13	
AST (15-41 U/L)	normal	52.00±30.15	0.272
	elevated	91.00±26.87	
ALT (7-35 U/L)	normal	54.25±31.79	0.530
	elevated	50.50±3.53	
BUN (8-20 mg/dL)	normal	53.44±31.49	0.578
	elevated	65.0±21.21	
Creatinine (0.4-1 mg/dL)	normal	52.91±31.79	0.246
	elevated	67.33±15.53	
CK (38-234 U/L)	normal	46.15±27.81	0.029*
	elevated	71.16±31.53	
Lactate (0.5-2.2 mmol/L)	normal	47.00±31.53	0.056
	elevated	66.14±26.77	
aPTT (20-35 sn)	normal	51.20±30.20	0.069
	elevated	87.33±20.03	
INR (0.85-1.2 INR)	normal	51.29±29.27	0.351
	elevated	66.28±37.47	
PT (11-15 sn)	normal	51.29±29.27	0.351
	elevated	66.28±37.47	

SD: Standard deviation, Hb: Hemoglobin, PLT: Platelet, AST: Aspartate transaminase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, CK: Creatinine kinase, APTT: Activated partial thromboplastin time, INR: International normalized ratio, PT: Prothrombin time *: Significant values

mediastinitis. Surgical debridement may be required in these cases. In a study conducted in 2017 in South Africa, Wagener et al. (6), a total of 164 patients included a study, of whom 57 required surgical debridement. Forty-two patients had positive cultures. Thirty-five specimens (83.3%) grew Gram-negative Enterobacteriaceae, the most frequent being Morganella morganii and Proteus species detected by Microbiological analyses. None of our patients required surgical debridement. Celulitis was the most common infection which was controlled by ampiric antibiotic treatment. We believe that our management with profilactic antibiotics in patients with wrong first aid measures helped low serious infection rate (6,7).

In a study conducted in 2001 in Brazil, Ribeiro et al. (8) reported that tourniquet use was related to serious tissue necrosis in *Bothrops jararaca* (Brazilian pit viper) envenoming cases. Pressure immobilisation bandages are recommended in envenoming except for some snake species that can cause local tissue oedema (9,10).

In a study conducted in India in 2008, Suchithra et al. (11) reported that wrong implementation is the major problem in pressure immobilisation. They concluded that this aid causes time loss for snakebite patients. Nearly all the patients' first aid involved a tourniquet in our study; thus, we could not compare tissue necrosis in patients with and without tourniquets.

Of the 38 study patients, the 20 who were overweight were affected more seriously and hospitalised longer (64.35±31.77 hours vs 42.61±26.31). Hyperglysemia, skin and soft tissue infections, are prevalent in the obese patients, which are expected in this population (12). Obesity is found to correlate with prolonged hospitalization which may be due to delayed wound healing and comorbidities of obese patients.

The major problem we realised in snakebite cases was the time loss during applying, referral and transportation to the adequate clinic for treatment. Patients should be evaluated for staging according to the envenomation presentation and given antivenom as quickly as possible. We calculated the time interval between snakebite and antivenom administration to prove the effectiveness of the early administration of antivenom in neutralising the toxic effects of venom. Our patients were evaluated quickly, and antivenom was given at a proper dose after staging. Low bite-to-needle time was correlated with low hospitalisation.

In a study by Sharma et al. (13) conducted in east Nepal in 2004, mortality was found to be correlated with hospital admission time after envenomation. Suchithra et al. (11) also reported a correlation of complication frequency with hospital admission time after envenomation.

There are two strategies on antivenom usage in snakebite treatment, namely, the traditional high-dose versus current low-dose antivenom administrations. Studies conducted in our region reported the effectiveness of low-dose antivenom in the successful treatment of snakebite (14). In their study in India, Das et al. (15) compared the effectiveness of high and low doses in a study and reported that low doses are as effective as high doses and lead to early patient discharge. Stage 2 and three patients were given 3.33±1.29 and 4.40±1.14 vials, respectively, in our study. All the study patients were cured with low doses.

Antivenom may cause serious allergies. As reported in one study, despite premedication, the rate of allergy after antivenom is 17.8% in our region (14). Although no premedication was given to our study patients, only one anaphylactic reaction was observed. The antivenom infusion was stopped, anaphylaxis was treated properly and a quick recovery was achieved. The current antivenoms seem to be less allergic than the old ones were.

The hemotoxic effects of our region's snakes may lead to coagulopathy. FFP was given to the patients in stage 3 in whom expected recovery could not be achieved with antivenom in the treatment of coagulopathy. In 2013, Isbister et al. (16) reported that, in patients with coagulopathy, FFP given as an additive to antivenom helped correct coagulation abnormality but had no effect on early discharge. We also could not find any relationship between FFP usage and hospitalisation duration.

In a study reported in 2016, Li et al. (17) demonstrated that elevated CK and low hemoglobin (Hb) are correlated with snakebite-related acute renal failure. Athappan et al. (18) reported that, intravascular hemolysis, cellulitis, regional lymphadenopathy, more than 2 hours of admission (bite-to-needle time), hypotension, massive bleeding were independent risks for renal disfunction in a series of 159 snakebite patients.

High CK and low Hb may be accepted as markers of serious envenomation, leading to longer hospitalisation. We report the long hospitalisation durations of patients with low platelets and low Hb, as well as elevated CK, which is compatible with the literature. In a study conducted by Ozay et al. (19) in 2005, low platelets were found to lead to more complications as well as longer hospitalisations. The researchers also reported that a platelet level <100,000/mm^3 was a high risk factor.

Study Limitations

The cases of this study were all from The Mediterranean Region. The snake species seen in Turkey are similar in all regions. This study is performed in only one center in The Mediterranean Region which is the major limitation of the study.

Conclusion

There are many harmful, wrong and improperly implemented first-aid measures that cause damage in snakebites. Public education is needed in this matter. The antibiotic usage rate is high because of wrong first aid. The association between shorter bite-to-needle times and shorter hospitalisation durations shows the importance of early administration of antivenom. Low-dose antivenom is effective in snakebite cases and allergy is extremely rare. The long hospitalisation durations in overweight patients may reflect a slower healing process in snakebite cases due to co-morbidities. The long durations of hospitalisation in patients with low platelets, low haemoglobin and elevated CK may lead to interpretation of these markers as poor prognostic indicators.

Ethics

Ethics Committee Approval: This study was approved by Çukurova University Faculty of Medicine Noninvasive Clinical Researches Ethics Committee (decision no: 5, date: 05.07.2013).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: M.Ö., A.A., Data Collection or Processing: M.Ö., A.A., U.A., Ö.T., Analysis or Interpretation: M.Ö., A.A., U.A., N.R.D., A.S., Ö.T., Literature Search: M.Ö., A.A., U.A., N.R.D., A.S., Ö.T., Writing: M.Ö., A.A., U.A., N.R.D., A.S., Ö.T.

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