ORIGINAL ARTICLE

Snakebite Prognostic Factors: Leading Factors of Weak Therapeutic Response Following Snakebite Envenomation

BITA DADPOUR[1], AZAM SHAFAHI[2], SEYED MOSTAFA MONZAVI[1,3], ABBAS ZAVAR[1], REZA AFSHARI[1,*], ALI REZA KHOSHDEL[3]

[1] Addiction Research Centre, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Department of infectious diseases, Intensive care unit, Mashhad University of Medical Sciences, Mashhad, Iran
[3] AJA University of Medical Sciences, Tehran, Iran

Abstract

Background: The goal of antivenom administration for snake-bitten patients is to achieve therapeutic response (initial control), which means reversal of the venom-induced effects through neutralizing the venom. The aim of this study was to identify snakebite prognostic factors of weak therapeutic response prior to antivenom administration.
Methods: This was a retrospective study of patients with viperidae snakebite envenomation who were admitted to Mashhad Toxicology Centre during 2007-2011. Demographic features, clinical manifestations and snakebite severity score (SSS) were collected prior to antivenom administration. Total number of antivenom vials administered to achieve therapeutic response and duration of hospitalization were also recorded. Potential factors in snakebite prognosis were analyzed by comparing in two groups of achieving therapeutic response with less than 5 vials and over 5 to calculate odds ratio.
Results: Total of 108 patients (male/female: 85/23) with mean (SD) age of 34.5 (17.0) were studied. The most common manifestations included fang marks (100%), pain (100%), ecchymosis (89%), swelling (83%), blister formation (48%) and thrombocytopenia (25%). In univariate analysis, thrombocytopenia (P=0.01), spontaneous bleeding (P=0.02), coagulopathic disturbances (P=0.007), swelling (P=0.003), progressive swelling (P=0.005), ecchymosis (P=0.05) and respiratory distress (P= 0.05) were significantly correlated to weak therapeutic response. Swelling and spontaneous bleeding were the strongest snakebite prognostic factors, as respectively they put the patients at 12.4 and 10.4 fold risks for difficult achievement of therapeutic response.
Conclusion: In snakebite, some clinical manifestations in the first hours of admission and prior to antivenom administration are associated with weak therapeutic response. Identifying these prognostic factors, can assist health care providers to better estimate the patient's needs and predict the final consequences.

Keywords: Snakebite; Prognostic factor; Thrombocytopenia; Therapeutic response; Initial control

INTRODUCTION

Snakebite in Iran is a major health problem, which affects approximately 4500-6500 individuals with 3-9 deaths each year according to recent reports of Iranian Ministry of Health and Medical Education (1). In Khorasan Razavi catchment area, 30 to 70 snakebites occur annually which are mainly because of two viperidae snakes, Echis carinatus and Vipera lebentia (1-3). Most of these victims were being admitted to Imam Reza Hospital, Mashhad Medical Toxicology Centre (MTC), a multidisciplinary reference department for management of poisoned patients in northeastern Iran. Less than 1% mortality rate has been reported among them (1,3).

Viperidae envenomations are mostly known to cause coagulopathic disturbances (mucosal and internal hemorrhages, thrombocytopenia and decrease in coagulation factors) in addition to local effects (pain, progressive edema, erythema, ecchymosis, bulla and blister) and other systemic effects (nausea, vomiting, dyspnea, neurologic abnormalities, hypotension, shock) (4,5). Extensive or progressive local effects, severe systemic and hemostatic abnormalities are the main indications of antivenom administration (3,4). Annual internal reports (MTC) showed that approximately 90% of these patients received antivenom during admission. The goal of antivenom administration for snake-bitten patients is to achieve therapeutic response (initial control) which means reversal of the venom-induced effects (cessation of edema progression and improvement of systemic manifestations) through neutralizing the venom.

Razi™ polyvalent antivenin is the only commercially available treatment for snakebite in Iran and is approved by Iranian Ministry of Health and Medical Education (5). It is a F(ab')2 antivenom product which is derived from equine hyperimmune serum and capable of neutralizing the venom of 6 most common snakes in Iran including 5 viper species (Echis carinatus sochureki, Vipera lebetina obtusa, Vipera albicornuta, Agkistrodon halys, Pseudocerastes persicus)

[*] Correspondence to: Reza Afshari, Addiction Research Centre, Mashhad University of Medical Sciences, School of Medicine, Mashhad, Iran.
Tel: +98 511 859 8973, Fax: +98 511 852 5315, E-mail: afsharir@mums.ac.ir
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and an elapidae species (Naja naja oxiana) (6,7). This product has been efficiently used in treatment of snakebite with limited adverse effects. The manufacturer has recommended administering 1-2 vial attack doses until stabilizing the patient or reversal of venom effects (5,6). However, local experience through past 4 decades in MTC revealed that morbidities and mortalities are higher with such lower initial doses (3). Therefore, according to a locally developed grading scale (Table 1), for patients with moderate envenomation up to 4 vials, for severe cases 5-9 vials and for very severe cases 10-15 vials were being administered to achieve therapeutic response. Half of the initial dose was also being added if no response was attained in the first hours (3). Notwithstanding, in recent years, as a more conservative practice, lower attack doses (<10 vials) have been administered even to patients with very severe envenomation.

Although most of venom-induced effects will be subsided after average of 4-5 vials antivenom (3,8), some victims might experience progression of effects and require higher doses. Identification of characteristics of these patients will help clinicians to better estimate and decide the amount of antivenom needed and the duration of admission. Furthermore, it assists health policy makers to more accurately predict sufficient antivenom supplies for such patients. The objective of this study was to investigate snakebite prognostic factors of weak therapeutic response prior to antivenom administration.

METHODS

This was a retrospective cross-sectional study of definite or suspected cases of viperidae snakebite envenomation according to taken snake corpse or patient's clinical manifestations who were admitted to MTC during 2007-2011. Exclusively those patients who received antivenom as part of their treatment were enrolled. Demographic features, clinical manifestations and laboratory examinations prior to antivenom administration, snakebite severity score (SSS) (9), total number of antivenom vials administered, duration of admission of each patient according to available medical records were collected. To be included in the data analysis, each record had to include complete documentation to assess all potential factors and allow calculation of SSS. Snakebite severity score is a validated measure for evaluation of crotaline snakebites (a subfamily of viperidae snakes) severity according to local edema, hematologic tests, and gastrointestinal, neurologic, respiratory and cardiovascular signs (9). The ultimate SSS score ranges between 0-20, while snakebites with 0-3 scores can be interpreted as mild, with 4-7 scores as moderate and over 8 as severe (9).

Data analysis was performed with Statistical Package of Social Sciences (SPSS Inc., Chicago, IL, USA). All potential factors in snakebite prognosis such as age, gender, bite site, venom induced manifestations and severity of snakebite were analyzed independently according to mean number of administered antivenom vials and duration of admission by univariate analysis and also linear regression model to find the strength of their relationship. Moreover, we considered 5 vials antivenom as cutoff point of difficult achievement of therapeutic response (weak therapeutic response). Accordingly, the potential factors were further analyzed by comparing in two antivenom groups (≤5 and >5 vials).

RESULTS

In this 5-year study, 108 patients were included which 79% of them were male. The mean (SD, range) age was 34.5 (17.0, 6-78) years. The antivenom except one patient, who developed mild hypersensitivity reactions, was administered with excellent safety and the median (range) of antivenom vials administered was 5 (1-25) during median of 2 days (1-7) of admission (Table 2). Most patients had mild to moderate envenomation according to SSS and the median of SSS was 2 (0-8). Approximately all patients were bitten in extremities with similar frequency in upper (50%) and lower (49%) and the anatomical location of bites were predominantly hand (44%) and foot (29%).

The most common manifestations included fang marks (100%) (Figure 1), pain (100%), ecchymosis (88.9%), swelling (83.3%), blister formation (48.1%) (Figure 2), thrombocytopenia (25%), nausea/vomiting (13%), dizziness (12%), respiratory distress (12%), abdominal pain (9.3%), tachycardia (7.4%), hypotension (5.6%), spontaneous internal or mucosal bleeding (5.6%), fever (4.6%), increased protimes which is recently known as venom-induced consumption coagulopathy (VICC) (10) (3.7%), and neurologic abnormalities (2.8%).

Through univariate analysis, it was ascertained that patients with significantly longer duration of admission had cardiovascular manifestations (P= 0.03), GI manifestations

Table 1. Snakebite severity grading

Grading	Local manifestation	Systemic manifestation
Minimal	Fang marks, no pain and swelling	None
Moderate	Swelling from bite site to adjacent joint, progressive swelling	None
Severe	Swelling involving entire bitten limb, blister/bulla formation, ecchymosis	None
Very Severe	Swelling beyond the bitten limb, extensive local necrosis, compartment syndrome	Incoagulable blood, increased protimes, thrombocytopenia, spontaneous bleeding, hemodynamic instability, shock, respiratory failure, acute renal failure, rhabdomyolysis, loss of consciousness

Figure 1. A severely envenomated patient following viperidae (*Echis carinatus*) snakebite. (with permission)
A. The patient was unable to open her eyes due to extensive edema. Ecchymosis and blister formation were also present. Arrows show the bite site (fang marks). The edge of edema was marked on the victim's face with a blue line. The patient later developed thrombocytopenia and VICC.
B. Same patient in the 4th day post-bite after administration of 24 vials of snake antivenom and other supportive treatments.

(P=0.03), progressive swelling (P=0.04) and more severe envenomation (P=0.01) prior to antivenom administration (Table 2). Moreover, it was demonstrated that patients with progressive swelling (P=0.01), respiratory distress (P=0.02), ecchymosis (P=0.04), thrombocytopenia (P=0.001), spontaneous bleeding (P=0.04), coagulopathic abnormalities in general (P=0.001) and also those with more extensive swelling (P<0.001) and severer envenomation according to SSS (P<0.001) significantly needed more antivenom to recover (Table 3). Putting these factors to stepwise linear regression model, after excluding confounding factors, revealed that a patient with swelling requires 4.2 fold, with progressive swelling 3.1 fold, with respiratory distress 3.2 fold and with coagulopathic disturbances 1.7 fold more antivenom to confine venom effects (number of antivenom vials= 1.8 + 4.2 [swelling] + 3.1[progressive swelling] + 3.2 [respiratory distress] + 1.7[coagulopathic disturbances], P= 0.02).

For better understanding the effect of each potential factor on snakebite prognosis, they have been further analyzed by comparing in two antivenom groups of requiring less than 5 vials and over 5 vials to achieve therapeutic response (Table 4). Thrombocytopenia (P=0.01), spontaneous bleeding (P=0.02), coagulopathic disturbances (P=0.007), swelling (P=0.003), progressive swelling (P=0.005), ecchymosis (P=0.05) and respiratory distress (P=0.05) were significantly correlated to weak therapeutic response. Swelling and spontaneous bleeding were the strongest snakebite prognostic factors, as a patient with swelling had 12.4 and with spontaneous bleeding had 10.4 fold risk for difficult achievement of therapeutic response (>5 vials) (Table 4).

DISCUSSION

Clinical condition of snakebite victims principally depends on the amount of injected venom into subcutaneous tissue or systemic circulation (3,4,11). Although local manifestations such as edema, ecchymosis and pain are observed in majority of cases, systemic manifestations which are more serious, solely develop in smaller proportion of patients (4,11). In this study, we found that pain, ecchymosis and swelling were the most common manifestations which were similar to the findings of Frangides et al. in Greece (12). We also found that critical systemic manifestation such as spontaneous bleeding, hypotension and neurologic abnormalities had rarely occurred in our patients comparable to the study of Frangides et al. (12).

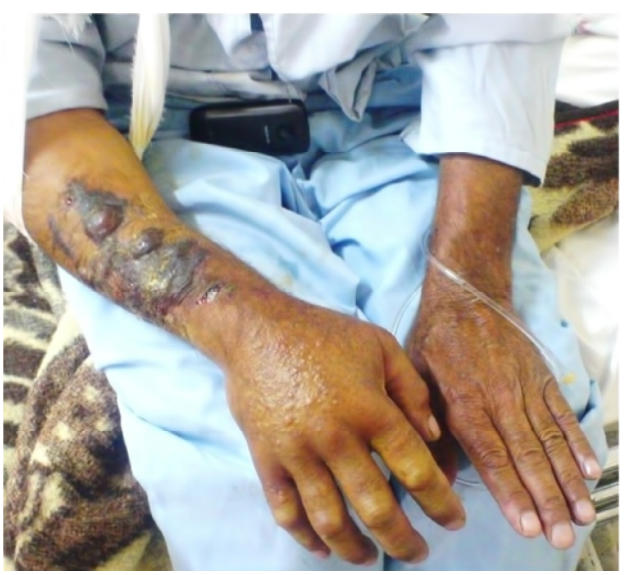

Figure 2. Severe edema, blister formation and dermal necrosis following viperidae snakebite. (with permission)

Table 2. Demographic data and clinical findings of 108 patients.

Feature	Scale	Report	Results
Gender	Male/Female	No. (%)	85/23 (78.7/21.3)
Age	Year	Mean ± SD	34.5 ± 17.0
Antivenom	No. vials	Median (IQR)	5.0 (5.0-10.0)
Weak therapeutic response	Patient	No. (%)	38 (35.2)
Adverse reactions	Patient	No. (%)	1 (0.9)
Duration of admission	Day	Median (IQR)	2.0 (2.0-3.0)
SSS	Score	Median (IQR)	2.0 (1.0-3.0)
PT	Second	Median (IQR)	13.0 (12.5-13.67)
PTT	Second	Median (IQR)	28.0 (26.0-31.0)
INR	IU	Median (IQR)	1.1 (1.0-1.2)
Platelet count	Count/L	Mean ± SD	184.2±57.9

Table 3. Univariate analysis of potential snakebite prognostic factors according to amount of antivenom, duration of admission and snakebite severity

Factor		Frequency	Antivenom	Duration of Admission	SSS
Gender	Male	85 (78.7%)	6.2 ± 3.6	2.4 ± 1.2	1.8 ± 1.3
	Female	23 (21.3%)	8.7 ± 6.3	3.0 ± 1.6	2.3 ± 1.8
	P Value		0.11	0.09	0.19
Respiratory distress[a]	Present	13 (12%)	10.7 ± 7.3	3.3 ± 1.9	3.3 ± 1.8
	Absent	95 (88%)	6.2 ± 3.6	2.4 ± 1.2	1.7 ± 1.2
	P Value		0.02*	0.21	0.001*
Cardiovascular signs[b]	Present	10 (9.3%)	7.6 ± 4.3	3.2 ± 1.0	2.5 ± 1.5
	Absent	98 (90.7%)	6.7 ± 4.4	2.5 ± 1.3	1.8 ± 1.4
	P Value		0.42	0.03*	0.187
Swelling	Absent	18 (16.7%)	2.3 ± 0.8	2.3 ± 1.1	0.2 ± 0.5
	≤7.5 cm	65 (60.2%)	6.7 ± 3.2	2.4 ± 1.2	1.9 ± 1.0
	7.5-50 cm	23 (21.3%)	9.6 ± 4.8	3.0 ± 1.7	3.1 ± 1.4
	50-100 cm	2 (1.9%)	15.0 ± 14.1	3.5 ± 0.7	4.0 ± 0.0
	>100 cm	0 (0%)	---	---	---
	P Value		<0.001*	0.22	<0.001*
Progressive swelling	Present	17 (15.7%)	10.3 ± 6.9	3.4 ± 1.9	3.3 ± 1.7
	Absent	91 (84.3%)	6.1 ± 3.4	2.4 ± 1.1	1.6 ± 1.2
	P Value		0.01*	0.04*	<0.001*
Ecchymosis	Present	96 (88.9%)	7.1 ± 4.5	2.6 ± 1.3	2.0 ± 1.4
	Absent	12 (11.1%)	4.3 ± 1.2	2.1 ± 0.9	0.9 ± 0.6
	P Value		0.04*	0.31	0.004*
Blister/Bulla	Present	52 (48.1%)	7.4 ± 4.5	2.8 ± 1.5	2.4 ± 1.5
	Absent	56 (51.9%)	6.2 ± 4.2	2.3 ± 1.0	1.4 ± 1.1
	P Value		0.15	0.07	0.001*
Gastrointestinal manifestations[c]	Present	17 (15.7%)	8.3 ± 5.8	3.2 ± 1.7	3.3 ± 1.8
	Absent	91 (84.3)	6.5 ± 4.1	2.4 ± 1.2	1.6 ± 1.2
	P Value		0.27	0.03*	<0.001*
Neurologic manifestations[d]	Present	3 (2.8%)	8.0 ± 2.6	2.6 ± 0.5	3.0 ± 1.7
	Absent	105 (97.2%)	6.7 ± 4.4	2.5 ± 1.3	1.9 ± 1.4
	P Value		0.42	0.61	0.25

Table 3. Continued

Factor		Frequency	Antivenom	Duration of Admission	SSS
Fasciculation	Present	2 (1.9%)	8.5 ± 4.9	3.0 ± 0.0	2.5 ± 2.1
	Absent	106 (98.1%)	6.7 ± 4.4	2.5 ± 1.3	1.9 ± 1.4
	P Value		0.46	0.37	0.67
Location of bite	Upper extremity	54 (50%)	6.2 ± 4.1	2.3 ± 1.04	1.7 ± 1.2
	Lower extremity	53 (49.1%)	7.4 ± 4.6	2.8 ± 1.5	2.1 ± 1.6
	Head & Neck	1 (0.9%)	5.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0
	P Value		0.35	0.07	0.33
Snakebite severity[e]	Mild	77 (71.3%)	4.9 ± 2.3	2.3 ± 1.0	1.2 ± 0.7
	Moderate	30 (27.8%)	10.9 ± 4.4	3.1 ± 1.5	3.6 ± 0.7
	Severe	1 (0.9%)	25.0 ± 0.0	7.0 ± 0.0	8.0 ± 0.0
	P Value		<0.001	0.01	<0.001
VICC[f]	Present	4 (3.7%)	9.7 ± 4.1	2.5 ± 2.3	3.2 ± 1.2
	Absent	104 (96.3%)	6.7 ± 4.4	2.5 ± 1.2	1.8 ± 1.4
	P Value		0.11	0.37	0.04
Thrombocytopenia[g]	Present	27 (25%)	8.7 ± 4.0	2.6 ± 1.3	3.0 ± 1.1
	Absent	81 (75%)	6.1 ± 4.4	2.5 ± 1.3	1.5 ± 1.3
	P Value		0.001	0.85	<0.001
Spontaneous internal or mucosal bleeding[h]	Present	6 (5.6%)	9.1 ± 3.5	3.0 ± 1.6	2.6 ± 1.3
	Absent	102 (94.4%)	6.6 ± 4.4	2.5 ± 1.3	1.9 ± 1.4
	P Value		0.04	0.44	0.15
Coagulopathic disturbances[i]	Present	31 (28.7)	8.5 ± 3.9	2.5 ± 1.2	2.9 ± 1.1
	Absent	77 (71.3)	6.1 ± 4.4	2.5 ± 1.3	1.5 ± 1.3
	P Value		0.001	0.94	<0.001

[a] Tachypnea (respiratory rate >20 breaths/min) and/or dyspnea and/or chest tightness and/or need for mechanical ventilation
[b] Hypotension (SBP<100) and/or tachycardia (heart rate>100) and/or dysrhythmia
[c] Nausea/ Vomiting and/or abdominal pain and/or diarrhea
[d] Dizziness and/or confusion and/or paresthesia in area of bite site and/or seizure and/or loss of consciousness
[e] According to SSS score
[f] INR > 2.0 and/or PT > 24 sec and/or unclottable blood by 20 min whole blood clotting time (20WBCT)
[g] Platelet count < 150,000
[h] Gingival bleeding and/or epistaxis and/or GI bleeding and/or hemoptysis
[i] VICC and/or Thrombocytopenia and/or Spontaneous bleeding.

Treatment of snakebite envenomation is mainly based on antivenom administration, though it is not advocated for all patients, especially those with only fang marks without any systemic or local manifestations (dry bites) (11,13). The ultimate goals of snakebite treatment are stabilization of patient and reversal of venom-induced effects (5,11,13). Consequently, it can be assumed that the total number of antivenom vials administered indicates the worseness of patient's condition and somehow determines the severity of snakebite. Identification of which clinical manifestations have the potential effect on requiring more antivenom to achieve therapeutic response or in other words inducing a poorer prognosis was the main objective of present study. We found that thrombocytopenia, spontaneous internal or mucosal bleeding, coagulopathic disturbances, swelling, progressive swelling, ecchymosis and respiratory distress are the risk factors of difficult achievement of therapeutic response. Likewise, in a recent study in the United States, Yin et al. ascertained that thrombocytopenia, coagulopathy, spontaneous bleeding, neurologic effects and severe bites were the main factors associated with difficulty achieving initial control (14). They also found that coexistence of thrombocytopenia and neurologic effects are with 13.8 fold risk of more difficulty in achieving initial control (13). In this study, we found that the presence of swelling and spontaneous bleeding are independently with 12.4 and 10.4 fold risk for difficult achievement of therapeutic response.

Viperidae snake family is known to possess fatal venoms which chiefly contain hemotoxin and vasculotoxin components (4,5,8). Hence, coagulopathic disturbances (spontaneous bleeding, thrombocytopenia and VICC) are predictable complications following their envenomation (10,15). The basic mechanisms of snakebite coagulopathy are known to be consumption of coagulation factors, platelet

Table 4. Odds ratio of potential factors of weak therapeutic response

Factor	Odds ratio	P Value
Gender	1.9	0.15
Respiratory distress	3.4	0.04
Cardiovascular signs	1.9	0.31
Swelling	12.4	0.003
Progressive swelling	4.3	0.005
Ecchymosis	7.2	0.05
Blister/Bulla	1.8	0.13
Gastrointestinal manifestations	1.8	0.26
Neurologic manifestations	3.8	0.28
Fasciculation	1.8	1.0
VICC	5.9	0.12
Thrombocytopenia	3.1	0.01
Spontaneous internal or mucosal bleeding	10.4	0.02
Coagulopathic disturbances	3.2	0.007

aggregation and ATP release by platelet aggregating proteins, platelet inactivation due to binding of venom antigens to platelet integrins, and damage to blood vessels which in most cases, they can be restored excellently and rapidly after antivenom administration (10,14-19). However, thrombocytopenia seems to resolve with difficulty as we found that in the presence of thrombocytopenia the victim has 3.1 fold risk of difficulty to achieve therapeutic response while similarly in the study of Yin et al. this risk was shown to be 3.6 fold (14). It has also been reported that recurrence of thrombocytopenia after initial control is not an uncommon phenomenon (20,21). To explain this problem, it has been proposed that the responsible venom components to cause thrombocytopenia are too small to be bound by antivenom immunoglobulin and in addition, these components might not be immunogenic enough to animals used in antivenom production process (14,22). Therefore, it has been concluded that antivenoms are not well effective to treat this complication.

Although it has not been completely studied, direct destruction of platelet and platelet precursors has been the other proposed mechanism (15,23). In consequence, a sharp reduction in platelet numbers would occur and despite antivenom administration, it prolongs the time to stop the problem and return platelet count to normal.

Swelling was also found to be the other prominent factor of weak prognosis in snakebite envenomation. It can be developed in almost all victims and unreasonably more than any other manifestations, it concerns clinicians (11,13,24). Sometimes, despite antivenom administration, swelling progresses and thus encourages clinicians to administer more vials. Nevertheless, it has been considered that the progression of swelling might be due to other mechanisms rather than direct effect of venom (24). Otero-Patino proposed that swelling is a spontaneous phenomenon of subcutaneous cell death due to inflammatory cytokine release following venom injection and can be persisted active for several hours even if the venom is neutralized (24). Consequently, he recommended excluding edema from therapeutic response definition at least for the first 24 hours post-bite (24). Accordingly, it is better to assume swelling as a factor of delayed response rather than a serious prognostic factor. Hence, if the only manifestation is swelling with no risk of compartment syndrome and it is not adjacent to high risk locations such as head and neck, it would be more appropriate to be treated supportively with conservative amounts of antivenom.

LIMITATIONS

In this study, following factors have constrained the validity of our findings. Since we retrospectively collected the data, the SSS was not mentioned in medical records as its evaluation is not a clinical routine. Therefore, the severity score was assessed retrospectively by the panelists' judgment.

Moreover, during the study period the clinicians were required to treat victims according to our accepted grading scale (Table 1). Therefore, higher doses of antivenom have been administered to patients with severer clinical manifestations and thus considering the number of total antivenom vials as an outcome might bear a bias implication. Nevertheless, as we mentioned, more conservative attack doses (<10 vials) of antivenom have been administered to very severe cases in recent years and also the antivenom has been repeated in cases with no therapeutic response, and so, the total number of antivenom can generally show the severity of manifestations. Furthermore, as we were unable to identify all offending snake species, this factor has been omitted from analysis and modeling. Hence, for future studies, obtaining this important piece of information is necessary. In addition, we had mostly mild and moderate cases and only two severe cases were found (Table 3). Consequently, our findings might be different from studies with predominantly including severe envenomation subjects.

Finally, this study comprised subjects who were admitted to MTC in northeastern of Iran with a dry semi-temperate climate and thus our findings might not be attributable to subjects from other geographical characteristics with different snake species (25).

CONCLUSION

In conclusion, we found some clinical manifestations including coagulopathy and swelling in the first hours of admission, before antivenom administration, associated with weak therapeutic response in snakebite. These findings can assist health care team to better estimate the patient's needs and predict the final consequences.

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