

Evaluation of antivenom therapy in *Vipera palaestinae* bites

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Abstract

Background: *Vipera palaestinae* antivenom has been successfully used to treat systemic and progressive local manifestations inflicted by this snake. The clinical course of several envenomations created the impression that the recommended fixed dose regimen of antivenom (50 ml) may not always be sufficient.

Objective: To evaluate the *V. palaestinae* antivenom fixed dose regimen and to assess the need for repeated antivenom administration as well as possible adverse effects.

Methods: Retrospective review of prospectively collected poison center data over a one-year period.

Results: One hundred and twelve patients were evaluated, 48% of whom were treated with antivenom. Antivenom treatment resulted in complete disappearance of systemic manifestations with no relapse. Three patients required additional doses of antivenom for marked progressive local signs—one initially received 50 ml of antivenom and two others only 30 ml. Anaphylaxis and serum sickness were each observed in 3.7% of the treated patients.

Conclusion: The fixed dose regimen of 50 ml *V. palaestinae* antivenom is efficacious for the treatment of systemic and progressive local manifestations caused by this snake. There is insufficient data on whether smaller doses can be successfully used for systemic manifestations and whether initial larger doses are justified for marked progressive local signs (e.g. involvement of an entire limb). Randomized prospective controlled studies are needed to elucidate these issues.

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1. Introduction

Northern and central Israel, southern Lebanon and the two banks of the Jordan River are inhabited by the venomous snake, *Vipera palaestinae* (Kochva, 1998; Shulov et al., 1987). It is responsible for most of the venomous snakebites in Israel (Bentur et al., 1997; Bentur and Cahana, 2003). The venom contains mainly enzymatic polypeptides, among them hemorrhagins, proteases, phospholipase A₂, hyaluronidase, esterases, phosphodiesterase and L-amino acid oxidase (Winkler et al., 1993; McKay et al., 1970; de Vries et al., 1967; Grotto et al., 1967).

The local and systemic manifestations of *V. palaestinae* venom are the result of the action of the above enzymes, i.e. endothelial damage, increased capillary permeability, platelet aggregation and dysfunction, thromboplastin and thrombin inhibition, some degree of fibrinolysis and hypofibrinogenemia, release of histamines and kinins and, possible, although not proven in humans, depression of medullary autonomic vasoregulation (Efrati, 1979; McKay et al., 1970; Grotto et al., 1969; de Vries et al., 1967; Krupnick et al., 1968; Grotto et al., 1967).

Anti-*V. palaestinae* equine antivenom has been in use for more than 40 years for treating envenomations with systemic signs and marked progressive local signs (Bentur et al., 1997; Bentur and Cahana, 2003; Efrati, 1962; Mann, 1980; Moroz, 1998). Although the efficacy of the *V. palaestinae* antivenom has been shown previously (Efrati, 1962; Bentur et al., 1997; Paret et al., 1997),

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the clinical impression produced by the clinical course of some envenomations is that the recommended dose (a fixed dose regimen) may not always be sufficient, and repeated administration of the antivenom may be required. This can result in greater morbidity and prolonged hospitalization.

The objective of this study was to evaluate the fixed dose *V. palaestinae* antivenom regimen recommended by our poison center and to assess the associated need for repeated antivenom administration and adverse effects. The results are expected to serve as a basis for considering a multicenter study to evaluate the most appropriate *V. palaestinae* antivenom regimen.

2. Methods

The study was conducted as a retrospective review of prospectively collected poison center data. All consultations at the Israel Poison Information Center, Rambam Medical Center, are provided by specialized physicians. Data are recorded on a comprehensive structured form. It includes caller and patient demographic details, route, site and circumstances of exposure, time elapsed to consultation, clinical manifestations in a detailed system-oriented approach, evaluation, management and follow-up recommendations. The severity of snakebite envenomations is graded as none, minimal (local swelling at bite site and other local changes, no systemic reactions), moderate (swelling progressing beyond site of bite with some systemic reaction and/or laboratory changes) and severe (marked local reaction with rapidly progressing edema, severe systemic manifestations and marked laboratory abnormalities; [Ellenhorn et al., 1997](#); [Dart et al., 1996](#)). In addition, the exposures and the causative agents are classified according to a previously prepared list of categories, classifications and subclassifications that is available at the poison center. Follow-up telephone calls are made by the consultants whenever possible, especially in antivenom-treated patients. Subsequently, all data are entered into a dedicated computerized database using Access 97 on a SQL server. All data are subjected to routine quality control. The Israel Poison Information Center is the national center of Israel and the only one that serves both the general public and healthcare facilities 24 h a day.

The poison center management recommendations for *V. palaestinae* bites include immobilization, observation and supportive measures. Corticosteroids are not recommended, nor is routine use of antimicrobial agents. *V. palaestinae* equine antivenom (Felsenstein Medical Research Institute, Rabin Medical Center, Beilinson Campus, Petah Tikva, Israel; [Moroz, 1998](#)) is indicated for systemic signs and marked progressive local signs even late in the course of envenomation ([Bentur et al., 1997](#)). The recommended antivenom dose is 50 ml administered as a 2 h IV infusion, preceded by a very slow test dose over 10 min.

Systemic signs, progression of local manifestations, complete blood counts and coagulation profiles are monitored during antivenom administration and over a 24-hour period thereafter. Additional antivenom doses (30–50 ml) may be given as dictated by the clinical course of the envenomation ([Bentur et al., 1997](#)). Repeated consultations and reports to the poison center are encouraged.

The study period included data collected in the course of one year. All poison center medical records classified as Biologicals/Snakes/*V. palaestinae* were retrieved. Diagnosis of *V. palaestinae* bite was made by history of bite and identification of the snake by individuals who were familiar with the local snakes and by means of photographs. Probable diagnosis of *V. palaestinae* bite was suggested by history of snakebite in the geographical area where it is the sole venomous snake as well as typical local findings, i.e. progressive local swelling, ecchymosis and bullae ([Bentur et al., 1997](#); [Bentur and Cahana, 2003](#)). Snakebite victims from the Jordan Valley, which is inhabited by the venomous *Echis coloratus* were not included. The geographical area concerned, northern and central Israel, is inhabited by non-venomous snakes of the families *Typhlopidae* (e.g. *Typhlops simoni*), *Boidae* (e.g. *Eryx jaculus*) and *Colubridae* (e.g. *Coluber jugularis* and *Coluber ravergeri*; [Barash and Hoofien, 1977](#)).

Each record was manually reviewed and analyzed for date of bite, patient's age and gender, geographical area of bite, time elapsed from bite until consultation, affected limb (upper or lower), systemic and local manifestations and abnormal laboratory findings, severity of envenomation, antivenom administration (indication, time to therapy, dose and adverse effects) and repeated antivenom administration, where applicable.

Data were transferred to an electronic spreadsheet (Excel 2000) and subjected to descriptive analysis and evaluation of subgroups. Data are expressed as median, mean $\pm$ SD and range. Chi square analysis was applied where relevant.

3. Results

During the one-year study period, a total of 301 calls pertaining to snakebites were received by the poison center; 171 calls were due to *V. palaestinae* bites. These calls related to 112 patients.

The distribution of patients according to geographical location was 50% in northern Israel, 48% in central Israel and for 2% of the patients, the exact geography could not be obtained. No bite of *V. palaestinae* was reported from southern Israel, as expected from the known geographical distribution of this snake ([Shulov et al., 1987](#); [Kochva, 1998](#)). Most bites (75%) occurred between May and October with a prominent peak in July–August (36%).

The median age of the victims was 26 years (30.8 ± 19 years, 1.5–76 years).

Table 1
Frequency distribution of toxic events caused by *V. palaestinae*

Toxic event	% of victims
<i>Local signs</i>	
Swelling	71
Fang marks	46
Pain	28
Redness	10
Ecchymosis	3.5
<i>Systemic signs</i>	
Vomiting	27
Abdominal pain	14
Nausea	8
Diarrhea	6
Tachycardia	11
Hypotension	10
Anaphylactoid reaction	1
<i>Laboratory</i>	
Thrombocytopenia ^a	3
Leukocytosis ^b	0.5
Anemia ^c	0.5

Patients could have exhibited more than one toxic event.

^a Range 89,000–109,000 μ l.

^b WBC > 10,000 μ l.

^c Hb 10.6 g/dl.

Gender distribution showed 68.7% males and 30.4% females; in one patient, gender was not reported (0.89%). The median time elapsed from the bite until consultation was 3 h (9.5 ± 15.3 h, 10 min–96 h). Upper and lower limbs were affected in 51.5 and 47.9%, respectively; one patient (0.89%) was bitten on the trunk.

Clinical manifestations were evident in 95.9% of the victims; of these 43.3, 2.3 and 50.3% had local only, systemic only and combined manifestations, respectively. The distribution of toxic events is shown in Table 1.

Swelling, fang marks and gastrointestinal signs accounted for most of the clinical manifestations. Swelling was noted in the area adjacent to the bite (27%), first, second and third large joints proximal to the bite (41, 28 and 3.2%, respectively) and on the trunk (0.8%). Frequency distribution of clinical severity showed 4.1% of the patients to be asymptomatic; 47.4, 43.2 and 5.3% suffered from minimal, moderate and severe envenomations, respectively. No significant difference in severity was found between males and females and between upper and lower limb envenomations.

Of the 112 victims, 54 (48%) needed antivenom. The indications for antivenom administration were moderate to severe local signs (29%), systemic signs (31%) or both (40%). Swelling involved the entire limb in 12.5% and gastrointestinal manifestations were the most common systemic effects in the antivenom-treated patients.

The median time elapsed from bite to antivenom administration was 3 h (8.1 ± 12 h, 0.5–56 h). The median amount of antivenom administered was 50 ml (49.5 ± 3 ml, 30–50 ml). Twenty patients did not require antivenom on presentation. The subsequent appearance of systemic signs, marked progression of swelling, or both, necessitated the initiation of antivenom therapy.

Following administration of antivenom, complete resolution of systemic and local signs ensued within hours in 54 (100%) and 51 (94.4%) treated patients, respectively.

Three (5.6%) out of 54 antivenom-treated patients required an additional dose of antivenom. The characteristics of these patients are shown in Table 2. In two patients, the first dose administered was lower than recommended. The indication for repeated antivenom dose, in all three patients, was progression of local manifestations; none had recurrence of systemic signs.

Of the 54 antivenom-treated patients, eight (15%) suffered adverse reactions. Six patients (11.1%) developed acute reactions within 60 min. Anaphylaxis occurred in two

Table 2
Characteristics of patients who required repeated antivenom therapy

Age (years)/gender	Site of bite	Local signs	Systemic signs	Time from bite to antivenom	Antivenom dose (ml)	Indication for second antivenom dose	Time between antivenom doses (h)	Second dose of antivenom (ml)
27/M	Palm	Swelling involving the elbow	Nausea vomiting	12 h	30 ^a	Swelling progressing to shoulder	13	50 ^b
36/F	Palm	Swelling involving the elbow	None	Several hours	30	Swelling progressing to shoulder	24	40
33/M	Palm	Swelling involving the elbow	None	2 h	50	Swelling progressing to shoulder	12	50

^a Initial recommendation was 50 ml, but pain at the injection site required cessation of antivenom after 30 ml.

^b Swelling eventually involved the trunk, necessitating a third dose of 40 ml.

patients (3.7%); it manifested as hypotension and bronchospasm and was treated with epinephrine. The other acute reactions were minor and included chills (2), fever (1) and pain at the injection site (1). Two patients (3.7%) developed serum sickness around 8 days after being treated with the antivenom. Neither had acute side effects nor required repeated antivenom administration.

4. Discussion

The results of this study show that *V. palaestinae* bites were inflicted more often in the summertime. Toxicological consultation was sought early, 3 h. The patients were mainly young adults; males were affected twice as often as females. The bites were distributed almost evenly between the upper and the lower limbs. The vast majority of patients were symptomatic, as expected in a specialized tertiary referral center. Almost all symptomatic patients had local signs and about half of them had systemic manifestations. The frequency distribution by clinical severity showed only a minor percentage of severe envenomations contrary to older studies (Efrati, 1962; Mann, 1980).

This difference can be explained by increased awareness as to the necessity of early arrival to a medical facility, early institution of therapy, improvement in intensive care measures and different methodology of data collection.

In this study, the fixed dose of antivenom administered resulted in complete disappearance of systemic manifestations in all patients without any recurrence. In addition, no patient suffered from compartment syndrome or bullae. Only one patient needed an additional dose of antivenom above the 50 ml of the fixed dose regimen—because of progression of local signs. In the two other patients who required additional antivenom, the initial dose was 60% of the recommended dose (Table 2). These findings indicate that the fixed dose regimen is adequate in terms of dosage and timing (median of 3 h from envenomation).

It should be mentioned that in some studies on *V. palaestinae* bites, the administered dose was not specified (Efrati, 1979; Mann, 1980; Winkler et al., 1993; Paret et al., 1997). In a survey of 125 victims of *V. palaestinae* bites, the antivenom dose administered varied between 10 and 60 ml. Although a dose smaller than 40 ml was regarded as having questionable efficacy and a 50–80 ml dose was generally recommended, no data were provided to substantiate this (Efrati, 1962). In a more recent study, a 20 ml dose given to patients with systemic manifestations abolished the manifestations in 63% of patients. The rest of the patients needed additional doses of up to 80 ml. In 7% of the antivenom-treated patients, a relapse was observed within 3–12 h after the initial positive response (Shemesh et al., 1998). Comparison of the results of the stepped regimen (Shemesh et al., 1998) to the fixed dose regimen used in our study strongly implies that the stepped regimen shows no obvious

benefit over the fixed dose regimen. The question remains whether the safety profile provides any advantage. In the stepped regimen, 9.3% of patients developed anaphylaxis to the antivenom and 44% had serum sickness. In our study, anaphylaxis occurred in 3.7 and 3.7% developed serum sickness.

In another study on *V. palaestinae*-envenomated children treated with an unspecified dose of antivenom, no anaphylaxis or serum sickness were reported. Mild adverse reactions (skin rash and fever) were reported in 40.5% of the patients (Paret et al., 1997) versus 7.4% in our study. An older study reported urticaria in 3% and serum sickness in 6.5% after antivenom therapy (Efrati, 1962). In two studies, one patient developed urticaria and facial swelling out of 13 patients severely envenomated by *V. palaestinae* and treated with antivenom (Bentur et al., 1997; Bentur and Cahana, 2003). As these reports show, the stepped regimen was not safer than the fixed dose regimen.

We refrain from any further comparison of these studies as they were neither randomized nor controlled.

Anticrotalidae antivenom used to be given in a graded dose titrated to the severity of envenomation. Fab anticrotalid antivenom is currently administered in a different manner using the concept of initial control and subsequent scheduled doses at 6, 12 and 18 h (Dart and McNally, 2001). However, the correct dosage is difficult to determine as no controlled studies were published.

Our study is limited by its retrospective design and relatively limited follow-up data. This may have resulted in some underestimation of the rate of adverse reactions to the antivenom. In addition, it should be noted that although the clinical grading method is commonly used, it has not been validated and its use for clinical decisions is limited.

In summary, the fixed dose regimen of 50 ml *V. palaestinae* antivenom is efficacious for the treatment of systemic and progressive local manifestations inflicted by this snake.

Insufficient data are available on the possible efficacy of lower doses of antivenom for treating systemic manifestations and avoiding relapse.

It is unclear whether doses higher than 50 ml are justified for the initial treatment of marked progressive local manifestations (i.e. swelling involving the entire limb) or in patients who present late in the course of envenomation.

Randomized prospective controlled studies are required to determine the most adequate *V. palaestinae* antivenom dosage regimen in terms of both efficacy and safety.

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