



DOES HIGH DOSE OF VIPERIDAE SNAKE ANTIVENOM SHOW HIGHER EFFICACY OVER LOW DOSE IN SEVERE ENVENOMING?

RAGIA M. HEGAZY* ^(1, 2) **AND GHAZI A. BAMAGOUS** ⁽²⁾

¹ *Department of Forensic and Clinical Toxicology, College of Medicine, Benha University, Egypt*

² *Department of Pharmacology and Toxicology, College of Medicine, Umm Al-Qura University (UQU), Makkah, Saudi Arabia*

ABSTRACT

Snake bites poisoning is considered as one of the most common causes of death in Saudi Arabia annually. This study aimed to evaluate the efficacy of administration of high doses of anti-snake venom (ASV) versus low doses in adult patients with severe Viperidae envenoming. Cases were collected retrospectively from Dammam poisoning center, Saudi Arabia throughout the years: 2010 and 2012. Low doses treatment regimen was followed in year 2010 where a total of 4 to 6 vials of ASV were given distributed, while, in year 2012, high doses treatment regimen was followed in which the patients were given an initial infusion of 5 to 10 vials. These two methods were compared based on efficacy, number of vials, and complications. Data of 150 patients were collected, 114 (76%) of the recruited patients were males and 36 (24%) were females. The incidence rate of coagulopathy, and the need for packed RBCs were significantly less in high ASV doses in comparison to low doses ($P=0.002$ and $P=0.02$, respectively). The high doses of ASV appear to be safe and effective against the coagulopathy complications in severe snakes envenoming. This study concluded that patients with severe viperidae snake envenoming are preferred to receive high ASV doses to neutralize the circulating venom, and lower the occurrence of serious complications. The study recommends administration of 5-10 vials of ASV as an initial dose in severe snake envenoming is essential.

KEYWORDS: Snake bite; Anti-snake venom; Packed RBCs; Coagulopathy.



RAGIA M. HEGAZY

Department of Forensic and Clinical Toxicology,
College of Medicine, Benha University, Egypt
Department of Pharmacology and Toxicology, College of Medicine,
Umm Al-Qura University (UQU), Makkah, Saudi Arabia

*Corresponding author

INTRODUCTION

At least 421,000 cases of envenoming and 20,000 deaths occur every year worldwide due to snake bite ⁽¹⁾. Among developing countries, the highest rates of mortality and morbidity are observed in Asia ⁽²⁾. The currently available antivenom is produced against the most dangerous snakes species (families) including *Echis Carinatus*, *Najanajaoxiana*, *Viperalebetina*, *Viperaalbicornuta*, *Agkistrodonhalys* and *pseudocerastespersicus* (according to Razi brochure) (any reference). It is considered as the standard treatment protocol for the management of snakes envenoming cases in Saudi Arabia. The presently polyvalent anti-snake venom (ASV) is effective against bites of the hematotoxic (viperidae) and neurotoxic (elapidae) snakes, but it is expensive, and may be associated with allergic reactions in the blood. There is a tendency among physicians to use too small doses of ASV over high doses for the treatment of cases of severe snake envenoming, as they have proved to be a safe option of treatment in order to reduce the risk of development of allergic reactions compared to the high doses ⁽³⁾. ASV is mostly effective when used at the appropriate dosage and indication ⁽⁴⁾. Nevertheless, there is a conflicting advice among physicians about the appropriate dosing, frequency of administration and duration of therapy. Recommendation of a universal initial dose required to neutralize the circulating venom is a difficult issue, as there is no well-known end point available in antivenom administration against snake bite envenoming ^(5, 6). In Australia, the recommended initial dose is ranging from one to four vials of antivenom ⁽⁷⁾. Even when the venom is neutralized by antivenom, there is usually a delay before the coagulopathy state is recovered ⁽⁸⁾. Bite of a venomous snake is considered as a common and life-threatening emergency in the areas with warm months. Venomous snakes in these areas mainly have hemotoxic (viperidae) and/or neurotoxic (elapidae) venom ⁽⁷⁾. Poisoning Center in Dammam city has the largest caseload of seriously envenomed patients by bite in Saudi Arabia. According to its records, the hemotoxic (viperidae) snakebite is said to have accounted for about 30% of all bites or stings patients by venomous animals requiring stay at this Centre. This record reaches mostly 300 cases annually. Therefore, severe local snake envenoming is a common presentation to DPC (Dammam Poisoning Centre). Patients with venomous hemotoxic (viperidae) snake bites are usually admitted to the hospitals with signs and symptoms ranging from bleeding, sweating to life-threatening coagulopathy, renal failure and shock. Coagulopathy is a common and serious manifestation of severe snake envenoming ^(9, 10).

The aim of this study was to compare the effectiveness of two different dosage protocols of antivenom administration on the outcomes of patients with severe local snake viperidae envenoming particularly coagulopathy state.

SUBJECTS AND METHODS

This comparative and retrospective descriptive study was conducted on patients who were bitten by snakes then referred to DPC, Saudi Arabia. It was performed in two separated years: 2010 and 2012. The medical records of all recruited patients were reviewed at DPC. Snake envenoming was defined by patients' medical reports and correlation between clinical manifestations and recognition of snakes by patients and bystanders. Venom specific enzyme immunoassay was not available, so the snake species were identified in all cases through clinical presentation of the patients. In this study, polyvalent antivenom (equine origin) was used. For the prevention of hypersensitivity reactions against viperidae polyvalent ASV, corticosteroids, H₁ and H₂ antihistamine receptor blockers, and epinephrine were available at the patient's bedside if needed ⁽¹¹⁾. All patients with a confirmed diagnosis of severe snake envenoming were identified and recruited in this study.

For each patient, a report form was submitted by the nurse in charge, including the following studied parameters:

1 Epidemiological characteristics

- a) Demographic information: age, gender, and residence (rural or urban areas).
- b) Snake bite related information: time and site of bite.

2 Management related information

Numbers of used vials, interval time between bite and initiation of ASV administration, development of hypersensitivity reactions to ASV, development of coagulopathy complications, administration of FFP (fresh frozen plasma) and packed red blood cells and hospitalization period. After administration of 4 to 6 vials of ASV through intravenous infusion, Prothrombin time, fibrinogen level, and platelets counts were determined. The coagulopathy state was defined in the presence of platelets count of $<150,000/\text{mm}^3$, prothrombin time above normal, or fibrinogen level of $<150 \text{ mg/dL}$ conditions ⁽¹²⁾. This was followed by patient's evaluation for local injury. These parameters, in addition to clinical evaluation, were used for the purpose of screening for coagulopathy. For achieving control of the acute envenoming, maintenance dose of 2 vials of ASV was given every 6 hours for three times (low dose regimen). The control state was defined as arrest of local tissue manifestations and return of prothrombin time, fibrinogen level, platelet counts, and systemic signs to normal. When control state was obtained, the patient was discharged with a follow up appointment after three days; if control state was not achieved, the patient received an additional dose of ASV (high dose regimen). This study was approved by the Institute of Ethics Committee of the Faculty of Medicine, UQU, Makkah, Saudi Arabia.

STATISTICAL ANALYSIS

This comparison between the efficacy of the two dose regimens was achieved based on: number of used vials, FFP, and packed red blood cells (RBCs), hypersensitivity reactions to ASV, coagulopathy state, and hospitalization period. Statistical analysis of data was performed by SPSS 17 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean \pm standard deviation and the discrete variables as percentage. The Student's t test was used to find out the significance of difference between the means (numerical data). P value <0.05 was considered a statistically significant difference.

RESULTS

One hundred fifty cases were admitted to DPC, Saudi Arabia, due to severe snake bite poisoning throughout the years of 2010 and 2012. The patients recruited during the year of 2010 were treated with low doses of anti-snake venom (ASV) regimen, while those recruited during the year of 2012 were treated using high doses of ASV regimen.

1 EPIDEMIOLOGICAL CHARACTERISTICS

Table 1: Baseline data of patients with viperidae envenoming during the year of 2010 (n=78) and the year of 2012 (n=76).

		On 2010 (n=75)	On 2012 (n=75)	P-value	Total (n=150)
Gender	Male	50 (66.7%)	63 (84%)	=0.02*	113 (75.3%)
	Female	25 (33.3%)	12 (16%)		37 (24.7%)
Residence	Rural	51 (68%)	52 (69.3%)	$<0.05^*$	103 (68.7%)
	Urban	24 (32%)	23 (30.7%)		47 (31.3%)
Time of bite	Day	26 (34.7%)	30 (40%)	$<0.05^*$	56 (37.3%)
	Night	49 (65.3%)	45 (60%)		94 (62.7%)
Site of bite	Upper limb	15 (20%)	25 (33.3%)	=0.04*	40 (26.7%)
	Trunk	2 (2.7%)	0		2 (1.3%)
	Lower limb	58 (77.3%)	50 (66.7%)		108 (72%)

*P<0.05 was considered significant.

Among the recruited patients of this study (n=150), Most of the patients (n=120, 80%) aged between 15 to 30 years, 20 were females and 60 were males. Of the 150 patients identified with severe viperidae snake bites poisoning, males constituted 75.3% of the study population (n=113) compared to females (24.7%, n=37). In the year of 2010, males were 50 (66.7%) while females were 25 (33.3%). Males to females' ratio remained the same during the year of 2012 with males as 84 % (n=63) in comparison to females (16%, n=12). Statistically, male gender had a significant higher incidence of snake bite poisoning over female gender (P=0.02) (Table. 1). In terms of location of snakes bites, 108 (72%) of the included patients have been bitten on the lower limb, 40 (26.7%) have been bitten on the upper limb and the remaining two patients (1.3%) have been bitten on the trunk. Accordingly, the site of bites in lower limb was significantly higher (P= 0.04) in comparison with other sites (Table. 1). Many bites (n=103, 68.7%) took place in rural areas as shown in table (1). There was a significant difference (P<0.05) between rural and urban residence of cases with high incidence of rural residence. A significant statistical difference was observed with regard to the time of biting as the night time biting was significantly higher than day time biting (P=0.04) (Table. 1).

Table 2: Management data of patients with severe viperidae envenoming during the year of 2010 (n=75) and the year of 2012 (n=75).

Parameters	On 2010 (n=75)	On 2012 (n=75)	P value
Number of packed red blood cells	15 (20%)	3 (4%)	=0.02*
Number of FFP	28 (37.3%)	14 (18.7%)	=0.09
Number of ASV*	5.5 ± 1.7	21.06±10.89	=0.001*
Hypersensitivity reaction to ASV	8 (10.7%)	4 (5.3%)	=0.37
Hospital stay in days	3.5 + 0.91	3.5 + 0.9	=0.99
Coagulopathy complications	72 (96%)	26 (34.7%)	=0.002*

The number of used ASV and hospital stay in days were presented as Mean± standard deviation.

*P<0.05 was considered significant.

2 CLINICAL CHARACTERISTICS

Of the 75 cases sustaining severe envenoming during year 2010, patients who received packed red blood cell were 15 (20%), that was significantly higher (P=0.02) than 3 patients (4%) in the year of 2012 with similar treatment. Regarding the management using clotting factors (FFP and/or cryoprecipitate): in the year of 2010, treated cases constituted 28 (37.3%) compared to 14 cases (18.7%) in the year of 2012 without any statistical significant difference noticed (P=0.09) as illustrated in Table (2). The number of ASV vials received by patients was 5.5±1.7 and 21.06±10.89 in 2010 and 2012 cases, respectively. Doses of ASV received by patients with severe envenoming in year 2012 were significantly higher than those in year 2010 (P=0.001). In addition, neither hypersensitivity to ASV, nor period of hospitalization showed a statistical significant difference between the two regimens in terms of number of patients with snakes envenoming (P=0.37 and P=0.99, respectively) (Table. 2). The incidence rate for the need of prescribing packed red blood cells in year 2012 cases was significantly lower than cases in year 2010 (4% vs.20%, respectively) with a P-value of 0.02. The coagulopathy as a serious complication of snake envenoming was significantly reduced (P=0.002) in year 2012 cases compared to cases in year 2010. Coagulopathy complications as a whole was significantly higher in 72 cases (96%) in year 2010 compared to 26 cases (34.7%) in year 2012 as illustrated in table (2).

DISCUSSION

This study was conducted to compare the efficacy and complications of applying high versus low doses of ASV laboratory and clinically in patients with severe snake viperidae envenoming in two separate years. Snakes envenoming is one of the most important causes of fatal animals envenoming. This envenoming is commonly due to snakes of the Viperidae family, mainly *Echis Carinatus*. ASV is usually given to neutralize the venom procoagulants and antithrombotic

effects, restoration of the coagulability and accelerate platelets functions by giving FFP, fibrinogen and fresh whole blood or platelet concentrates⁽¹⁰⁾.

The measured parameters in this study included the following: number of packed FFP, number of packed RBCs given, coagulopathy state profile and hypersensitivity reaction to ASV. These parameters were routinely investigated to evaluate efficacy of antivenin treatment in cases of Viperidae snake bite. In the present study, the high number of used ASV vials to manage cases with severe envenoming in year 2012 was significantly more effective than low dose that was used in year 2010. Coagulopathy complications and the need of packed RBCs in year 2012 were significantly less than those of year 2010. These findings did not match with White et al., 2002; and Isbister et al., 2008^(13, 14) where they found no significant difference between low and high doses of ASV with regard to both hypersensitivity reaction to ASV and period of hospitalization. Our results had profound implications for high dose antivenom therapy for severe snake envenoming, at least that resulting from local snake bite. These results were supported by previous *in vitro*⁽¹⁵⁾, animal⁽¹⁶⁾ and clinical studies⁽¹⁷⁻¹⁹⁾ that recommended administration of large doses of ASV especially earlier in order to obtain an early recovery.

In disagreement with our results, Chieh et al., 2009⁽²⁰⁾ has found that the increase in the incidence of complications was associated with higher antivenom doses. Also, in other studies of Srikantet al., 2014⁽²¹⁾ and Cherian et al., 2013⁽²²⁾, small doses had equivalent effect when compared to large doses. Low doses even better, because they had fewer side effects, and mortality. Warrell, 2000⁽³⁾ explained an advantage of small doses of ASV over the large doses, by low cost, especially with the shortage of the ASV availability in developing countries. In a study conducted by Isbister et al., 2009⁽¹⁰⁾, it was found that factors other than doses could play a role in the choice of regimen protocol for the management of severe envenoming of snakes bites. They proved that time is an important factor especially in the case of a blood clot, regardless of the amount of ASV, describing that the best time to give the ASV is during the first hour.

Need for packed RBCs and development of coagulopathy problems in year 2010 (low dose regimen) was higher than year 2012 (high dose regimen), while significant difference in number of patient who needed FFP, hypersensitivity to ASV and duration of hospitalization was not detected. Our study showed that administration of FFP containing clotting factors should be necessary if a neutralizing dose of antivenom is administered. Furthermore, our results recommend that larger doses of antivenom are required for preventing a fibrinogenaemia for prolonged periods with serious consequences.

Tariang et al., 1999⁽²³⁾ supported our results where they found that neurotoxic envenomation requires higher dose of ASV, while Paul et al., 2004⁽²⁴⁾ reported that the mortality rate and the percentage of cases requiring dialysis are more in the higher dose of ASV in management of haematotoxic snakes. In a short report of Kasturiratne et al., 2008 in India⁽¹⁾, the effects of two different dosage protocols on the outcomes of patients with severe neurotoxic snake envenoming were studied. They suggested that low dose of snake antivenom is as effective as high dose in patients with severe neurotoxic snake envenoming.

The snake bites in eastern area of Saudi Arabia (where DPC is located) are predominantly caused by viperidae snakes with haematotoxic manifestations. As a result, there is an urgent demand to receive high dose of antivenom to overcome these complications. In the present study, 76% of the patients were males as compared to 24% as females. The ratio of male preponderance was also reported by various studies⁽²⁵⁻²⁷⁾. According to Hansdak et al., 1998⁽²⁵⁾, snakes bites were 2.5 times more common in males. Also, Meyer et al., 1997⁽²⁶⁾ found that 85% of patients with snakes bites were males. In the study carried out by Narvencar, 2006⁽²⁷⁾, 90% patients were males. This ratio may be probably due to the nature of occupation of men that used to be out-door particularly in the rural areas.

In terms of the timing of bite, this investigation demonstrated a higher incidence of biting at the nighttime than daytime, with a significant difference noticed. Al-Lawatia et al., 2009⁽²⁸⁾ reported that most of the bites took place in the afternoon or evening, whereas (Frangides et al., 2006)⁽¹²⁾ found that the largest incidence of bite was during the warmest midday hours. This study revealed a high incidence of snakes' bites in rural areas, an observation that has also been reported by other studies^(29, 30). This is probably due to the lifestyle and occupational exposure of the people living in these areas such as farmers or herdsman.

The site of snake bite has shown to be significantly higher in lower limbs of the patients compared to other parts of the body. A similar data has been observed in the study carried out by (Alavi and Alavi, 2008)⁽³¹⁾ over the period (1997– 2006), and showed 71.8% of snakes bites were on foot. This finding is also supported by other studies^(21, 32). ASV, particularly when given intravenously, not infrequently results in early reactions, ranging from rash and urticaria to fatal anaphylaxis. Pyrogenic reactions and late serum-sickness-type reactions can also cause distressing symptoms^(6, 14). As showed in our study, the administration of ASV has been safe since hypersensitivity reaction were seen in 8 cases (10.3%) and 4 cases (5.3%) following low versus high dose of vials administration in the 2010 and 2012 year, respectively. The high antivenoms doses were reported to be more allergenic, with acute reactions seen in more than 20% of patients^(33, 34). Our results also suggested that the incidence of serum sickness is unrelated to dose. This finding is on the contrary to previous studies and case reports of severe reactions to antivenin that believed it would be dose dependent which cause a fear of polyvalent antivenin therapy and reluctance by clinicians to administer high doses of antivenin^(33, 35, 36).

Following snake bite and receiving the treatment, there were no deaths, amputations, or lasting disability in the discharged patients. Therefore, the available ASV preparation is considered to be effective for the treatment of envenomation caused by all dangerous species of snakes such as those found locally.

From this study we concluded that high dose of ASV appears to be safe and effective for the coagulopathy complication in severe snakes envenoming. The titer and efficacy of ASV needs to be evaluated experimentally. It is recommended for the patients to receive high ASV doses to neutralize the circulating venom and remain more stable for long periods in order to lower the risk of development of serious complications. This study recommended that the administration of 5-10 vials of ASV as an initial dose in severe snake envenoming is essential. Cautious usage of high dose of ASV (10-20 vials) without highly special concerns on the cost are essential in the routine management of severe snake envenoming.

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