Research Article

Judicious use of antisnake venom in the present period of scarcity

Srikant R. Gadwalkar, N. Sunil Kumar, D. P. Kushal, G. Shyamala, M. Z. Mohammad, Huggi Vishwanatha

Abstract

Context: Although antisnake venom (ASV) has been used for many years, selection of an optimal dose is a debated issue due to acute shortage of ASV in India. Despite evidence for smaller doses, most centers still use conventional doses. **Aims:** This study aimed to evaluate the effects of two different dosage regimens on the outcome of patients with snake envenomation, using a retrospective descriptive analysis of patient records admitted in our hospital. **Settings and Design:** A retrospective descriptive case series study was conducted from hospital records consisting 155 snakebite patients from June 2013 to January 2014. **Materials and Methods:** Patients were divided into two groups: Low dose ASV group (received <10 vials) and high dose ASV group (received ≥10 vials). Various complications were compared among these two groups. **Results:** The mean dose of ASV used in high dose, and low-dose group was 14.7 ± 5.3 and 4.2 ± 2.3, respectively. In low dose group, 20.5% of patients had acute kidney injury, whereas it was 10.9% in high dose group. In low dose group, 12.3% patients had neuroparalysis severe enough to require ventilator support and mortality rate was 5.5% which was comparable to the high-dose group (15.8% had neuroparalysis requiring ventilator support and a mortality rate of 8.5%). **Conclusion:** This study demonstrated that the low dose ASV regimen in poisonous snake bites along with supportive treatment as necessary is as efficacious as high dose regimen and has comparable complications.

Keywords: Acute kidney injury, low dose antisnake venom, snake bite

Access this article online
Website: www.ijccm.org
DOI: 10.4103/0972-5229.144014
Quick Response Code:

Introduction

Background

Snake bite is a major health problem in India due to prevailing climatic conditions and the fact that major portions of the population are rural and agrarian. Envenoming by snakes is an occupational health hazard often faced by farmers and farm laborers of tropical and subtropical countries like India. Nearly 216 species of snakes are identified in India, of which 52 are known to be poisonous. Every year about 40,000-50,000 people die of snake bites in India.[1]

From:
Department of General Medicine, Vijayanagar Institute of Medical Sciences, Bellary, Karnataka, India

Correspondence:
Dr. Srikant R. Gadwalkar, Department of General Medicine, Vijayanagar Institute of Medical Sciences, Bellary, Karnataka, India.
E-mail: srikantbly@gmail.com

Importance

Patients with snake envenomation present as emergencies with significant morbidity and mortality. The only specific antidote for snakebite is administration of antisnake venom (ASV) with or without adjunctive treatment as necessary in each case. The issue which confronts the physician when attending to a patient with snakebite is assessment of the degree of systemic envenomation and decision on dose of ASV.

The hitch with determining the optimum ASV dose is that the quantity of venom injected at a bite is very variable, depending on the species and size of the snake, the mechanical efficiency of the bite, whether one or two fangs penetrated the skin and whether there were repeated strikes.[2] Furthermore, neutralization by antivenom must occur almost immediately after venom enters the circulation to significantly impact on recovery time of the coagulopathy due to envenomation.[3]

The Indian snake bite treatment protocol recommends an initial dosage of 10 vials of polyvalent ASV for adults and children.[4] This is based on published research that Russell's Viper injects 63 mg of venom on an average.[5] The range of venom injected is 5-147 mg. Logic suggests that our initial dose should be calculated to neutralize the average dose of venom injected. This ensures that the majority of victims should be covered by initial dose and keeps the cost of ASV to an acceptable level. According to the Indian snake bite treatment protocol, In case of hemotoxic poisoning repeat dose of ASV is, usually, required. The correction of coagulopathy is the most important criteria to continue the ASV treatment. After the first dose of bolus ASV, it should be repeated after 6 h depending on the coagulation profile and may be repeated till the coagulation profile is corrected. In neurotoxic poisoning after the first dose has been given, another dose may be repeated after 1 h provided the patients have not improved, or worsened. The suggestion of the total requirement of dosages lies between 10 and 30 vials of ASV. The presently available polyvalent ASV, one effective against bites due to common neurotoxic and hemotoxic snakes, is expensive and scarce-especially in high-risk areas.

Objectives

There have been no published dose-finding studies of ASV. Several studies in South India have compared low-dose ASV regimen to standard dose and found no difference in the outcome. There is no consensus on the dose of ASV required in the management of snake bite, and selection of a particular dose of ASV is a debated issue. Despite evidence for smaller doses from evidence-based medicine, most centers still use conventional/high doses according to national guidelines.

This retrospective case series study was conducted to demonstrate whether the whether the low and high dose regimens are comparable in efficacy in terms of survival and prevention of complications. This is particularly important in the context of the high cost and the at-risk population being poor farmers.

Materials and Methods

Study design and setting

This study is a retrospective hospital record-based descriptive analysis of patients treated in our hospital over a period of 8 months from June 2013 to January 2014. A total of 155 snakebite patients who were aged ≥15 years presented to our hospital between this time with signs and symptoms of local as well as systemic envenomation which included hemostatic abnormalities such as, spontaneous gastrointestinal bleeding, uncontrolled bleeding from external wounds, prolonged computed tomography (>20 min), prothrombin time (international nationalized ratio >1.5), activated partial thromboplastin time (>2× control), hypotension (blood pressure <90/60 mm of Hg), shock (requiring inotropic support), acute kidney injury (AKI) evidenced by oliguria, anuria, and rising serum creatinine. The 20 min whole blood clotting test was adopted as the standard test of coagulopathy. It is simple to carry out and gives a reliable indication of consumption coagulopathy.

For the neurotoxic poisoning, the most important criteria were clinically based. Neurotoxic signs included ptosis, diplopia, dysphagia and pooled secretions, external ophthalmoplegia, respiratory muscle paralysis–poor neck lift, falling single breath count, falling SpO_2, hypoxic symptoms such as cyanosis, altered sensorium, and coma.

Patients with urine output <0.5 ml/kg/h for >6 h or increased serum creatinine >1.5 times baseline or by a rise of at least 0.3 mg/dl were considered to have AKI according to AKI network criteria. Patients with severe hyperkalemia or symptomatic metabolic acidosis or pulmonary edema or uremic complications such as pericarditis, uremic encephalopathy were considered for dialysis. Patients with hypoxic symptoms like altered sensorium and coma or absence of gag reflex, cough reflex, falling saturation were considered for mechanical ventilation. All patients with signs of systemic envenomation were given ASV.

All patients with snake bite envenomation were treated with conventional dosage of ASV according to Indian snake bite treatment guidelines up to August 2013. But, due to acute shortage of ASV from the month of September 2013, we were instructed by the hospital authority to use ASV judiciously. We were forced to use lower dose of ASV, even in patients with severe envenomation and complications. We carefully monitored complications and intervened with appropriate alternative treatment options, supportive care and used further doses of ASV as and when available. This formed the basis of the study.

Methods and measurements

We made two groups from the snake bite cases. One group had received conventional dose (≥10 vials) from month of June to August 2013 and other group, had received low dose (<10 vials) from the month of September 2013 to January 2014. We compared different parameters among the two groups including various

complications and mortality rate. All patients who had received ASV before coming to hospital and patients in whom time of the bite to hospital was >48 h were excluded from the study group.

Outcomes

The complications in low-dose group (20.5% patients had AKI, 5.5% had AKI requiring dialysis and another 12.3% patients had neuroparalysis severe enough to require ventilator support and mortality of 5.5%) have been comparable to the high dose group, except for patients having AKI (10.9% in high dose group).

Statistical analysis

Data entered in Microsoft excel and analyzed using Statistical Package for the Social Sciences software (SPSS version 15.0,IBM SPSS inc., Chicago, IL.). Statistical analysis was carried out through following tests. Chi-square test and independent "*t*"-test were used as tests of significance. Chi-square test was used to compare categorical variable between two groups, that is, complications, fasciotomy, fresh frozen plasma (FFP), anaphylaxis, symptoms, and bite to needle. Independent "*t*"-test was used to compare mean values between two groups. Mean, standard deviation, median, interquartile range were used for descriptive analysis. *P* value is based on alpha and beta error. Alpha error is set to 5%, and beta error is set to 20%. So $P < 5\%$ is considered to be significant.

Results

The mean age of patients in the study was 39.5 ± 11.5 in high-dose group and 37.7 ± 11.4 in low-dose group. In the high-dose group, 52.4% were males and 47.6% were females, whereas in the low dose group, 47.9% were males, and 52.1% were females. About 78% of patients had bite in the lower limbs. The mean bite-to-needle time was 5.5 ± 3.7 h in high dose and 4.7 ± 3.4 h in low-dose group and mean duration of hospital stay was 4.1 ± 2.5 and 4.6 ± 3.0, respectively.

The mean dose of ASV used in high dose group was 14.7 ± 5.3 and a maximum of 30 vials in cases of severe hemotoxicity and spreading cellulitis. The mean dose of ASV in low dose group was 4.2 ± 2.3, and a maximum of eight vials was used when available. The clinical profile and demographic data among two groups are depicted in Table 1.

The complications in low-dose group (20.5% patients had AKI, 5.5% had AKI requiring dialysis and 12.3% patients had neuroparalysis severe enough to require ventilator support and mortality of 5.5%) have been comparable to the high dose group, except for patients having AKI (10.9% in high dose group). The various complications observed among two groups are compared in Table 2.

Most of the patients with AKI were treated conservatively (6 out of 9 [66.67%] in high dose and 11 out of 15 [73.34%] in low dose group). Only 3.6% patients in high-dose group and 5.5% of patients in low-dose group required dialysis, which was statistically insignificant.

Among patients with neurological complications, the percentage of patients who required ventilator support was comparable among both groups (9 out of 16 in low dose [56.25%] and 13 out of 27 in high dose group [48.14%]).

Patients requiring FFP for bleeding manifestations and fasciotomy for spreading cellulitis were higher in low dose group. Moreover, the incidence of early anaphylaxis and late serum sickness-type reactions was not related to dose of ASV, which is in contrary to other studies.[6]

Table 1: Comparison of demographic data and clinical profile among two groups

Parameters	Mean±SD (95% CI) (%)		*P*
	High dose ASV (*n*=82)	Low dose ASV (*n*=73)	
Age (years)	39.5±11.5 (37.02-41.99)	37.7±11.4 (35.13-40.3)	0.34
Bite-to-needle time (h)	5.5±3.7 (4.8-6.2)	4.7±3.4 (3.9-5.5)	0.15
Duration of hospital stay (days)	4.1±2.5 (3.5-4.6) (*n*=75)	4.6±3.0 (3.9-5.3) (*n*=69)	0.25
Symptoms			
Hemotoxic	42 (51.2)	41 (56.2)	0.53
Cellulitis	51 (62.2)	55 (75.3)	0.07
Neurotoxic	27 (32.9)	16 (21.9)	0.12
ASV vials used	14.7±5.3 (13.55-15.86)	4.2±2.3 (3.71-4.80)	0.001

SD: Standard deviation; CI: Confidence interval; ASV: Antisnake venom

Table 2: Comparison of various complications among two groups

Complications	High dose ASV (*n*=82) (%)	Low dose ASV (*n*=73) (%)	*P*
AKI (not requiring dialysis)	06 (07.3)	11 (15.0)	0.12
AKI with dialysis	03 (03.6)	04 (05.5)	0.70
Ventilator	13 (15.8)	09 (12.3)	0.39
Death	07 (08.5)	04 (05.5)	0.66
Mean of serum creatinine in patients with AKI (in mg/dl)	2.25 (median) 3.3 (IQR)	3.45 (median) 3.2 (IQR)	0.58
Days on ventilator support (in days)	4.0 (median) 4.5 (IQR)	1.5 (median) 3.5 (IQR)	0.23
Fasciotomy	00	02 (02.7)	0.22
FFP	02 (02.4)	07 (09.6)	0.08
Anaphylaxis	02 (02.4)	03 (04.1)	0.90

ASV: Antisnake venom; AKI: Acute kidney injury; FFP: Fresh frozen plasma; IQR: Interquartile range

Finally, there was no difference in mortality between the two groups.

To assess the effect of time elapsed between snakebite and initiation of treatment (an important confounding factor), the relationship between bite-to-needle time and complications were compared in Tables 3 and 4. In these tables, the bite-to-needle time was compared among various important complications in these two groups. Among them, AKI was more commonly observed among patients belonging to 4-6 h of bite-to-needle time in low dose group and was statistically significant ($P< 0.05$). Moreover, the quantity of antivenom used was independent of the bite-to-needle time except in low dose group, where patients who received ASV during early hours had lesser chances of AKI as shown in Tables 3 and 4.

Discussion

The mean dose of ASV used in our study was 14.7 ± 5.3 and 4.2 ± 2.3 in high- and low-dose group, respectively. Although there was a significant reduction in the dose of ASV used ($P= 0.001$), various complications like AKI, neuroparalysis requiring ventilator support, spreading cellulitis requiring fasciotomy and severe bleeding manifestations requiring FFP were comparable in both the groups as shown in Tables 1 and 2.

The mean bite-to-needle time, an important confounding factor for major complications, was also comparable among both groups. This was also similar to the studies done in South India such as Tariang *et al*.[7] in Vellore and Srimannarayana *et al*.[8] in Pondicherry. In a study conducted by Isbister *et al*., demonstrated that neither earlier administration of antivenom nor higher doses of antivenom reduced time to recovery of venom-induced consumption coagulopathy.[3,9]

Table 3: Comparison of relation between bite-to-needle time and complications in high dose group

Bite-to-needle time (h)	AKI (%)	AKI dialysis (%)	Ventilator (%)	Death (%)
1-3	02 (33.3)	00	02 (15.4)	02 (28.6)
4-6	03 (50.0)	01 (33.3)	06 (46.1)	02 (28.6)
7-9	00	00	02 (15.4)	01 (14.3)
>9	01 (16.7)	02 (66.6)	03 (23.0)	02 (28.6)
Total	06 (100)	03 (100)	13 (100)	07 (100)
P	0.33	0.21	0.32	0.93

AKI: Acute kidney injury

Table 4: Comparison of relation between bite-to-needle time and complications in low dose group

Bite-to-needle time (h)	AKI (%)	AKI dialysis (%)	Ventilator (%)	Death (%)
1-3	01 (10.0)	01 (25.0)	01 (20)	01 (25)
4-6	06 (60.0)	02 (50.0)	04 (80)	03 (75)
7-9	00	00	00	00
>9	03 (30.0)	01 (25.0)	00	00
Total	10 (100)	04 (100)	05 (100)	04 (100)
P	0.03	0.56	0.36	0.61

AKI: Acute kidney injury

In our study, a higher number of patients had developed AKI in low-dose group compared to a higher dose. However, it was statistically insignificant. Furthermore, most of the patients with AKI were treated conservatively. One of the reasons for a higher number of patients developing AKI in low-dose group could be due to late presentation to hospital as shown in Table 4. Hence, when there are adequate facilities available for dialysis and 24 h working nephrology unit as in our study hospital, low dose ASV would be a suitable option, even when patient has spreading cellulitis or impending oliguria.

Patients with neurotoxic bites requiring ventilator support was 15.8% and 12.3% in high and low dose group, respectively. The neurological complications are comparable to study done by Agarwal *et al*., which also showed no difference between a protocol employing lower doses of ASV to higher dose in the management of patients with "unselected" severe neurotoxic snake envenoming.[10] Furthermore, the mean duration of hospital stay was independent of the dose of ASV used, and most of the patients were discharged with similar duration in both the groups. This signifies similar rates of morbidity in both high and low dose groups, which again supports the benefits of using conserved doses of ASV.

Although ASV has been used for many years, there is no universal consensus in many centers on the optimal dose and protocol of its administration. Theoretically, it would appear that patients with more severe envenoming need higher doses of ASV for effective neutralization of circulating snake venom. However, many studies have shown that complications and mortality rates are comparable in patients receiving low dose. Thomas *et al*. showed a higher number of patients requiring ventilator support (7.4%) and slightly higher number of AKI cases (22.2%) with similar mortality rates in low-dose group (7.9 vials of ASV used) when compared to high-dose group (15.3 vials of ASV used).[11] In a study conducted by Paul *et al*., lower number of patients developed AKI in low dose group (18% vs. 26% in high dose) and 6% patients required ventilator support in both groups. Furthermore, mortality rate was slightly lower in low dose compared to high dose (10% vs. 14%).[12] In a more recent study conducted by Cherian *et al*., a low dose

of ASV was used (6.7 ± 3.24 vials). Among 54 patients, 12.9% patients developed AKI, 12.9% patients required ventilator support and mortality rate was 3.7%.[13] An apparent increased mortality rate in high dose group of our study can be explained by higher number of patients with neurotoxicity requiring ventilator support and other complications related to mechanical ventilation.

Large doses of ASV may not cause any improvement in patients with presynaptic neurotoxicity, which is probably due to the irreversible effects of these toxins (although the clinical significance of presynaptic inhibition is difficult to assess).[14] Moreover, due to the high cost and limited availability of ASV, and occasional reports of patients with severe envenomation recovering without the use of ASV, lower dose of ASV may be equally effective and is a considerable option in our Indian setup.[15]

Most of these studies were randomized trials done in India, which has shown little difference in complications between high and low dose ASV usage. This study is done in a tertiary hospital in the northern part of Karnataka, where most of the patients are farmers and has the highest number of snakebite cases in this part of India. This study also shows similar results in complications and mortality rate when compared to other studies as mentioned above.

Being a retrospective analysis is a major limitation of our study. But, the inclusion of the larger number of study patients as compared to previous studies conducted in India makes this study relevant and useful.[11-13] It may impact ASV usage in the future and provides sufficient evidence for many intensivists and physicians working in a rural setup to use ASV judiciously as required in a given case. Another drawback, like in other studies conducted in the past on low dose ASV, is that the optimum dose of ASV could not be determined.

In summary, this study has demonstrated that low dose ASV regimen in poisonous snake bites irrespective of the severity along with supportive treatment as necessary is as efficacious as high dose regime, and has comparable complications including death.

Many of the secondary and tertiary centers in almost all states of India are using lower doses of ASV due to acute shortage. This study was a simple way to analyze these controversies in using lower doses and has successfully shown that using a lower dose has no significant difference in complications and outcome including duration of hospital stay.

The economic significance of using low doses of ASV is obvious. Each 10 ml vial of ASV in India costs Rs. 410 and use of lower dosages could translate into huge savings to the patient and the community.[16] In addition, there is an increasing shortage of ASV in several developing countries and important incentive for a regulated dosing protocol would be to prevent the crisis of ASV availability and supply.[17,18]

In this era of rising medical expenditure and most of the countries facing shortage of ASV, further randomized trials are to be encouraged to determine lower and appropriate doses of ASV in management of snake bite cases. The Indian National Snakebite Protocol may also need to be reviewed taking into consideration these newer developments. Also newer areas should be looked into like development of more potent antivenoms with less toxicity, development of venom immunoassays for Indian subcontinent and use of immunoassays in dose-finding studies and development of recombinant antivenoms which will help in solving the problem of venom scarcity for the preparation of ASV.

References

1. Mohapatra B, Warrell DA, Suraweera W, Bhatia P, Dhingra N, Jotkar RM, *et al.* Snakebite mortality in India: A nationally representative mortality survey. PLoS Negl Trop Dis 2011;5:E1018.
2. Kumar BK, Nanda SS, Venkateshwarlu P, Kumar YK, Jadhav RT. Antisnake venom serum. Int J Pharm Biomed Res 2010;1:76-89.
3. Isbister GK, Duffull SB, Brown SG, ASP Investigators. Failure of antivenom to improve recovery in Australian snakebite coagulopathy. QJM 2009;102:563-8.
4. Indian National Snakebite Protocols 2007. Available from: http://www.scribd.com/doc/13591739/Snake-Bite-Protocol-2007-India. [Last accessed on 2014 Aug 25].
5. Tun PE, Khin Aung Cho. Amount of venom injected by Russell's viper (Vipera russelli). Toxicon 1986;24:730-3.
6. Theakston RD, Fan HW, Warrell DA, Da Silva WD, Ward SA, Higashi HG. Use of enzyme immunoassays to compare the effect and assess the dosage regimens of three Brazilian Bothrops antivenoms. The Butantan Institute Antivenom Study Group (BIASG). Am J Trop Med Hyg 1992;47:593-604.
7. Tariang DD, Philip PJ, Alexander G, Macaden S, Jeyaseelan L, Peter JV, *et al.* Randomized controlled trial on the effective dose of anti-snake venom in cases of snake bite with systemic envenomation. J Assoc Physicians India 1999;47:369-71.
8. Srimannarayana J, Dutta TK, Sahai A, Badrinath S. Rational use of anti-snake venom (ASV):Trial of various regimens in hemotoxic snake envenomation. J Assoc Physicians India 2004;52:788-93.
9. Warrell DA. Animal toxins. In: Cook GC, Zumla A, editors. Manson's Tropical Diseases. London: WB Saunders; 2003. p. 581-618.
10. Agarwal R, Aggarwal AN, Gupta D, Behera D, Jindal SK. Low dose of snake antivenom is as effective as high dose in patients with severe neurotoxic snake envenoming. Emerg Med J 2005;22:397-9.
11. Thomas PP, Jacob J. Randomised trial of antivenom in snake envenomation with prolonged clotting time. Br Med J (Clin Res Ed) 1985;291:177-8.
12. Paul V, Pratibha S, Prahlad KA, Earali J, Francis S, Lewis F. High-dose anti-snake venom versus low-dose anti-snake venom in the treatment of poisonous snake bites-a critical study. J Assoc Physicians India 2004;52:14-7.

13. Cherian AM, Girish TS, Jagannati M, Lakshmi M. High or low-A trial of low dose anti snake venom in the treatment of poisonous snakebites. J Assoc Physicians India 2013;61:387-9, 396.
14. Harris JB. Snake venoms in science and clinical medicine. 3. Neuropharmacological aspects of the activity of snake venoms. Trans R Soc Trop Med Hyg 1989;83:745-7.
15. Bomb BS, Roy S, Kumawat DC, Bharjatya M. Do we need anti snake venom (ASV) for management of elapid ophitoxaemia. J Assoc Physicians India 1996;44:31-3.
16. Ministry of Chemicals and Fertilizers, Department of Pharmaceuticls (National Pharmaceuticals Pricing Authority). Drugs price control order 2013. Website. http://www.pharmaceuticals.gov.in/dpco2013gaz.pdf; 2013;2:36-67.
17. Theakston RD, Warrell DA. Crisis in snake antivenom supply for Africa. Lancet 2000;356:2104.
18. Bawaskar HS. Snake venoms and antivenoms: Critical supply issues. J Assoc Physicians India 2004;52:11-3.

How to cite this article: Gadwalkar SR, Kumar NS, Kushal DP, Shyamala G, Mohammad MZ, Vishwanatha H. Judicious use of antisnake venom in the present period of scarcity. Indian J Crit Care Med 2014;18:722-7.

Source of Support: Nil, **Conflict of Interest:** None declared.