Research Article

A cross-sectional study to observe the effects of dose of anti-snake venom on outcomes and adverse effects in snake bite cases

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Abstract

Background: Snake bite is a major problem in rural India. The lack of universal consensus towards the dose of ASV to be used and dose-related adverse effects have been long-standing issues in the snake bite management protocols.

Objective: To observe the effects of dose of anti-snake venom (ASV) on outcomes and adverse effects in snake bite cases, in a rural tertiary care hospital in Maharashtra, India.

Materials and Methods: A cross-sectional observational study was carried out in the medicine intensive care unit (ICU) of SRTR GMC, Ambajogai by scrutinizing the prescriptions of 70 snake bite patients admitted to the ICU during the study period of 3 months. Data were analyzed using descriptive statistics and Microsoft Excel 2007. Statistical analysis was carried out using the Fisher's Exact test.

Result: Acute kidney injury developed in 6 (20%) and 9 (22.5%) patients, neuroparalysis requiring ventilator support developed in 4 (13.3%) and 6 (15%) patients, hospital stay duration was 1.36 and 2.92 days and the mortality rate was 3.3% versus 5%, in patients given low and high dose of ASV, respectively. But, the occurrence of adverse effects to ASV was significantly less with low dose of ASV.

Conclusion: Results were found to be comparable in terms of treatment outcomes. So, low doses of ASV can be utilized to optimize usage and minimize its adverse effects.

KEY WORDS: Acute kidney injury, anti-snake venom, neurotoxic, rural, vasculotoxic.

Introduction

Snakebite is a major problem in rural India with more than 2 lakh snakebite cases being reported in India annually of which 35,000–50,000 die.[1] A nationally representative study of 1,23,000 deaths from 6671 randomly selected areas conducted in 2001–2003, revealed an annual age-standardized rate of 4.1/1,00,000.[2] Globally, 1.2–5.5 million snakebites occur annually leading to as high as 18,41,000 envenoming and 94,000 deaths.[3]

The only specific antidote for snakebite is the administration of anti-snake venom (ASV) with or without adjunctive treatment as necessary in each case. The first reported successful use of antivenin serum therapy in patients was in 1896. It has been in use since then with a few formal clinical trials as to the right dose of antivenin required for treatment.[4]

Polyvalent (polyspecific) antivenoms are preferred in many countries because of the difficulty in identifying a particular snake species responsible for bites and they can be just as effective as monovalent (monospecific) ones. The one in India is developed against the four most important venomous snakes in India—Indian cobra (*Naja naja),* Indian krait (*Bungarus caeruleus*), Russell's viper (*Daboia russelii*), and

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saw-scaled viper (*Echis carinatus*). There is some cross neutralising activity also known, against venoms of closely related species.[5]

The polyvalent ASV (effective against neurotoxic and vasculotoxic poisons) is the mainstay of therapy. It is expensive and scarcely available, especially in high-risk areas.[5] Though ASV is the mainstay of therapy, there is no universally accepted standard regimen regarding the optimum dose, frequency of administration, and duration of therapy.

Ideally, the dose of ASV should be based on the measurement of serial venom concentrations in patients and determining when free venom concentrations are undetectable, but this is hardly clinically feasible.[6] That's why most recommendations are based on mouse assays, where the lethal dose is estimated to be around 120 mg of cobra venom and 60 mg of krait venom.[1] The amount of venom neutralized by 1 mL of ASV is around 0.6 mg for cobra and 0.45 mg for krait bite. Hence, the total empirical dose of ASV for a fatal cobra and krait bite is 200 mL and 134 mL, respectively.[7]

The WHO has recommended, which has been accepted by others, that the initial dose of Indian polyvalent ASV is 100 mL, that is, 10 vials of polyvalent ASV should be considered as initial dose of ASV in all types of snakebite in India.[5] It will neutralize 60 mg of Russell's viper venom and cobra venom; 45 mg of krait and saw-scaled viper venom, which will be effective in neutralizing major amounts of venom injected.

Another problem with ASV is that, it being an animal serum product, some patients develop hypersensitivity reactions to it. Usually more than 20% cases develop either early (within few hours) or late (5 days or more) allergic reactions following ASV administration. Thus, ASV though a life-saving drug, may cause serious adverse effects too and at times may confound the real cause of mortality in cases of snake bites. In addition, the lack of appropriate recommendations regarding prevention, diagnosis, and management of such adverse effects of ASV, further compound the problem.[8] This study was planned considering the prevalence of snake bites and its severity in a rural setup.

Materials and Methods

A cross-sectional observational study was carried out in the medicine intensive care unit (ICU) of Swami Ramanand Teerth Rural Government Medical College (SRTR GMC), Ambajogai, by scrutinizing the prescriptions of 70 snake bite patients admitted to the ICU during the study period of 3 months from July to September, 2015. Ethics approval was obtained from institutional ethics committee prior to initiation of the study.

All patients of snake bite admitted to medicine ICU of SRTR GMC, Ambajogai were included in this study. Those unwilling to participate in the study or with unproven or only suspected snake bite cases or patients with unknown bite were excluded from the study.

The data were collected on case record forms. The first section of the data included demographic details such as initials, age, gender, address, and occupation. The time and site of the bite were noted. The second section of data recorded—included the diagnosis in reference to the type of snake bite that is, vasculotoxic or neurotoxic—dose and duration of ASV administered. At last, number of patients developing acute kidney injury (AKI) due to renal toxicity of snake venom, those developing neuroparalysis requiring ventilator support, duration of hospital stay, and mortality from snake venom were taken into account as outcomes of treatment. Adverse effects reported to the ASV used were classified as early (anaphylactic, endotoxic, and pyrogenic) and late (serum sickness type) reactions.

Diagnosis of type of snake bite was made using the clinical signs and symptoms. Patients with vasculotoxic snake bites presented with bleeding from gums, gingival bleeding, epistaxis, prolonged bleeding from the bite site, hematuria, and extensive swelling whereas those with neurotoxic bites presented with ptosis, blurring of vision, diplopia, type II respiratory failure (hypoxemia with hypercapnia), dribbling of saliva from angle of mouth, nasal twang, and giddiness. Not all signs and symptoms were apparent in every patient. Sometimes there was a clinical picture suggesting combination of both vasculotoxic and neurotoxic snake bites. Data were analyzed using descriptive statistics and Microsoft Excel 2007. Statistical analysis was carried out using the Fisher's Exact test.

Result

The prescriptions of 70 snake bite patients admitted to medicine ICU during the study period were scrutinized. Maximum number of patients admitted, 67 of the 70 (96%), belonged to the rural areas in and around Marathwada, Maharashtra [Figure 1].

Males 39 (56%) predominated the list of snake bite victims admitted [Table 1]. Majority of cases [51 (73%)] of the snake bites occurred during the dark as against those occurring in broad daylight [Figure 2]

Lower limbs—mainly toes and area around the ankle joint was found to be the most frequent site of snake bite in 37 (53%) patients, closely followed by bite on upper limbs of 30 (43%) patients. Only three cases of snake bite in the thoracic area were reported [Figure 3].

Low dose of ASV (≤10 vials) was used in 30 (43%) patients and high dose of ASV (>10vials) was used in 40 (57%) patients of snake bite. In patients receiving low dose of ASV, 3 (4%) reported with rash and itching on upper limbs immediately after administration of the dose. In patients receiving high dose of ASV, 7 (17.5%) suffered from ASV-induced angioedema and 6 (15%) patients reported with fever, rigors, joint pain, and joint swelling. Thus, adverse effects were reported in three patients among those given low dose of ASV vis-à-vis 13 patients given high dose of ASV. This decrease in occurrence of adverse effects in patients receiving low dose of ASV was found to be statistically significant ($p = 0.04$, by Fisher's Exact test).

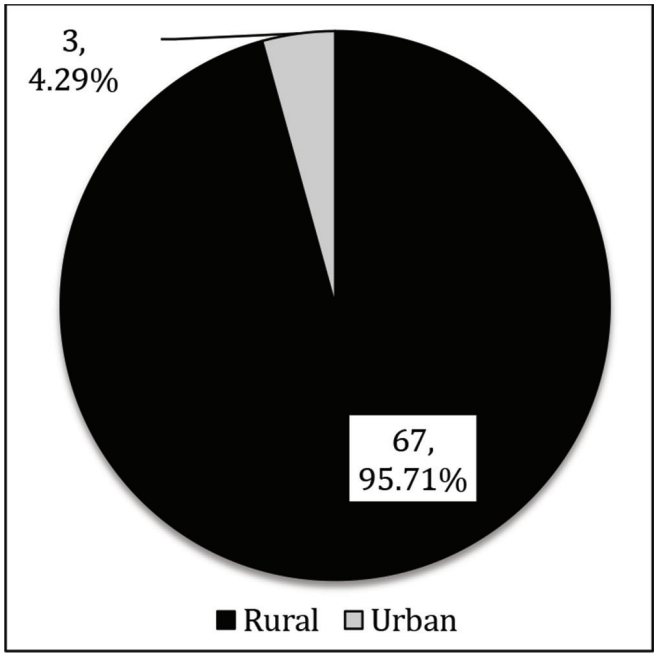

Figure 1: Residence-wise distribution of snake bite victims.

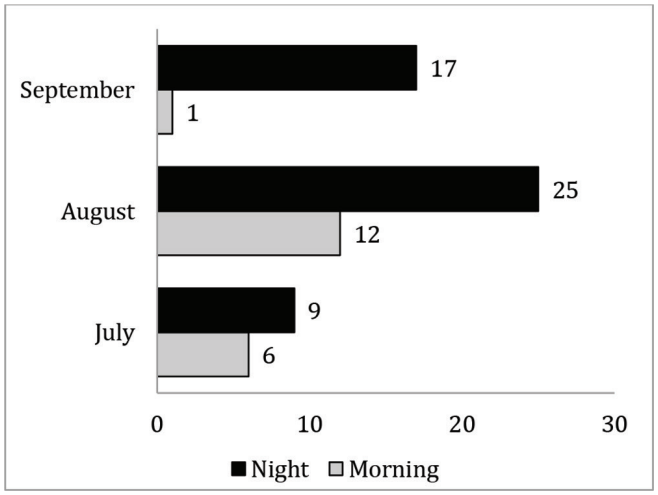

Figure 2: Number of snake bite cases with respect to time of the day.

Table 1: Gender-wise distribution of snake bite victims

	July 2015	August 2015	September 2015	Total
Males	06	24	09	39
Females	09	13	09	31
Total	15	37	18	70

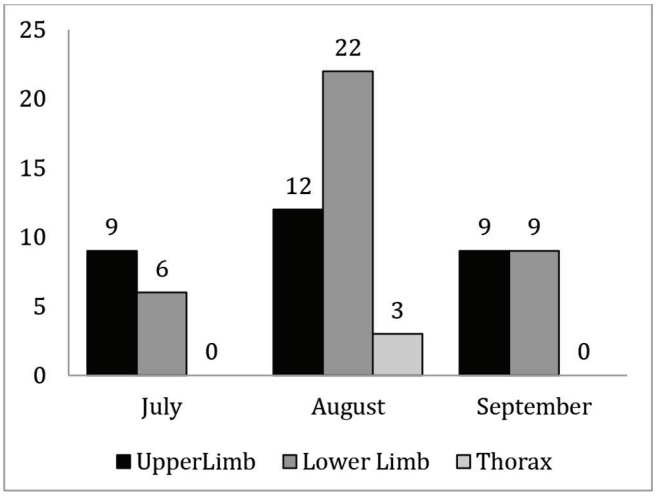

Figure 3: Anatomical distribution of snake bite.

Duration of hospital stay was found to be relatively low (average 1.36 days) in patients given low dose of ASV as compared to those administered high dose of ASV (average 2.92 days), in spite of all patients included in the study having comparable severity of signs and symptoms [Table 2].

Table 3 compares the outcomes of snake bite treatment in patients given low and high doses of ASV. Lesser number of patients [6 (20%)], receiving low dose of ASV, developed AKI, compared to those on high dose of ASV [9 (22.5%)]. This was however found to be statistically insignificant (p =1, by Fisher's Exact test). Four (13.3%) patients receiving low dose ASV and six (15%) patients receiving high dose ASV developed neuroparalysis severe enough to require ventilator. The mortality rate of 3.3% in patients who got low-dose ASV and 5% in those who got high-dose ASV was comparable (p = 1, by Fisher's Exact test).

Discussion

Snake bite is a common occupational hazard of farmers, plantation workers who are generally from low socioeconomic status, resulting in tens of thousands of deaths each year and many cases of chronic physical handicap. This explains the male predominance, rural preponderance, and the anatomical distribution of snake bite victims in our study, which is corroborated by findings of Agarwal et al.[7] (51% were male patients in their study).In our study, low dose of ASV (≤10 vials) was used in 30 (43%) patients and high dose of ASV (>10 vials) was used in 40 (57%) patients of snake bite. Various outcomes such as AKI, neuroparalysis requiring ventilator support, mortality were studied and found to be less in patients receiving low dose of ASV as compared to those receiving high dose of ASV though this difference was statistically insignificant (p = 1, by Fisher's Exact test) as shown in

Table 2: Parameters of patients with snake envenoming

Dose of ASV used	No. of prescriptions	Outcome	Duration of hospital stay in days (average)	Occurrence of adverse effect (no. of patients)
For patients with vasculotoxic signs and symptoms				
≤10 Vials	21	Full recovery	1.61	2 (9.5%)
>10 Vials	24	Full recovery	2.71	7 (29.2%)
For patients with neurotoxic signs and symptoms				
≤10 Vials	9	Full recovery	1.11	1 (11.1%)
>10 Vials	16	Full recovery	3.13	6 (37.5%)

Table 3: Measurement of complications in patients given low dose and high dose of ASV

	Acute kidney injury (AKI) [No. of patients]	Neuroparalysis requiring ventilator support [No. of patients]	Mortality
≤10 vials	6 (20%)	4 (13.3%)	1 (3.3%)
>10 vials	9 (22.5%)	6 (15%)	2 (5%)

Tables 2 and 3. This was comparable to findings of Tarang et al.[9] in Vellore and Srimannarayana et al.[10] (12.9% patients on low dose suffered from AKI vs. 25% patients on high dose suffering from AKI) in Pondicherry in south India.

Patients with neurotoxic bites requiring ventilator support was 15% and 13.3% in high- and low-dose groups, respectively. The neurological complications were comparable to the findings of Agarwal et al.[7] which also showed no difference between a protocol employing lower doses of ASV to higher dose in the management of patients with severe neurotoxic snake envenoming. In our study, the mean duration of hospital stay was a little less in patients given low dose of ASV compared to those given high dose ASV. This signifies similar rates of morbidity and mortality ($p = 1$) in both high- and low-dose groups, which again supports the benefits of using ASV conservatively.

Toxins from cobra venom predominantly act postsynaptically, whereas those of krait venom mainly act presynaptically. Postsynaptic (α) neurotoxins, such as α-bungarotoxin and cobrotoxin, consist of 60–62 or 66–74 amino acids. They bind to acetylcholine receptors at the motor endplate. Presynaptic (β) neurotoxins—such as β-bungarotoxin, crotoxin, and taipoxin—contain 120–140 amino acids and a phospholipase A subunit. These release acetylcholine at the nerve endings at neuromuscular junctions and then damage the endings, permanently blocking further release of neurotransmitter. However, most snake venoms contain both presynaptic and postsynaptic neurotoxins.[1,5,6] ASV is a specific antidote to the snake venom and is the only effective treatment for neutralization of venom that has entered the circulation. So, it would appear that patients with more severe envenoming need higher doses of ASV for effective neutralization of circulating snake venom. But, ASV neutralizes only circulating venom and it has no action once the venom is attached to the receptor site.[11]

Although ASV has been used for many years, there is no universal consensus in many countries on the optimal dose and protocol of its administration. However, many studies have shown that outcomes of treatment are comparable in patients receiving both high dose and low dose of ASV. Thomas et al.[12] reported a higher number of patients [6 (22.2%)] developing AKI in low-dose group (average7.9 vials) compared to 5 (19.2%) in high-dose group (average15.3 vials) with similar mortality rates in both the groups. One of the reasons cited for a higher number of patients developing AKI in low-dose group was late presentation to hospital. On the other hand, in a study conducted by Paul et al.,[13] lesser number of patients developed AKI in low-dose group [9 (18%)] versus 13 (26%) in high dose group and 3 (6%) patients required ventilator support in both groups. Furthermore, mortality rate was slightly lower in low-dose group compared to high-dose group (10% vs. 14%). In a more recent study conducted by Cherian et al.[14] only 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%, which is also suggestive of the fact that low dose of ASV could be effective and cause less adverse effects.Large doses of ASV may not cause any improvement in patients with presynaptic neurotoxicity, which is probably due to the irreversible effects of the snake venom on presynaptic nerve endings (although the clinical significance of presynaptic inhibition is difficult to assess).[15] Moreover, the cost of ASV and its availability is a problem. Each 10 mL vial of ASV in India costs between Rs. 200 to Rs. 500 and use of lower doses of ASV could translate into huge savings to the patient and the community. In addition, there is an increasing shortage of ASV in several developing countries.[1,16] Thus, it is imperative to evolve regulated dosing protocol to overcome the crisis of availability of ASV.

Occasional reports of patients with severe snake envenomation recovering without the use of ASV were also known.[17] In our study too, low dose of ASV was found to be as effective as high dose. However, high dose was associated with more adverse outcomes.

The WHO states that the anti-venom reactions are dose related.[5] Our study is also in agreement with findings of the WHO study, where patients receiving high dose of ASV developed significantly more adverse effects to ASV ($p < 0.05$) compared to those receiving low dose.

Conclusion

In an era of rising medical expenditure and with most countries facing an acute shortage of ASV, optimizing ASV usage and minimizing cost to the patient becomes an important aspect of treatment of snake bite cases. This study has demonstrated that the regimen employing low dose of ASV in poisonous snake bites, irrespective of the severity of the envenomation, along with supportive treatment, is as efficacious as high-dose regimen, and has comparable outcomes. Further randomized trials are to be encouraged to determine lower and appropriate doses of ASV in management of snake bite cases. Also, occurrences of adverse effects to ASV are comparatively less with low dose of ASV. Therefore, low doses of ASV can be utilized to optimize usage of available ASV stock and to minimize possible adverse effects to ASV which are of clinical significance. This would help reduce the burden on the already scarce ASV supply as also reduce cost incurred and discomfort faced by the patient.

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