THE EFFECT OF LOW VERSUS HIGH DOSE OF ANTI-SNAKE VENOM ON OUTCOMES AND ADVERSE EFFECTS IN SNAKE BITE CASES AT M.G.M. MEDICAL COLLEGE AND HOSPITAL, JAMSHEDPUR, JHARKHAND: A CROSS-SECTIONAL OBSERVATIONAL STUDY

Medicine

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ABSTRACT

Background: Snakebite is a significant problem in rural India. It is an occupational hazard and causes considerable morbidity and mortality. It is a significant financial burden on victims and hospitals. Fortunately, these bites are eminently treatable and curable. A lack of universal consensus for the dose of Anti Snake Venom (A.S.V.) exists. Low vs. high dose is the most debated topic. Dose-related adverse effects are enduring issues in the snake bite management protocols.

Objective: To observe the effects of the low and high dose of A.S.V. on results and side effects in snake bite cases in MGMM COLLEGE and hospital in Jharkhand, India.

Materials And Methods: We did a cross-sectional in the medical emergency and intensive care unit of M.G.M. Medical College, Jamshedpur. We analyze the prescriptions of 58 snakebite patients admitted to the I.C.U/emergency. We analyzed data during the study period of 3 months. We used descriptive statistics and Microsoft Excel 2007. Fisher's Exact Test is used to analyze statistically.

Result: A.K.I. was found in 5 (21%) low dose group and 9 (26%) high dose group, patients with neuromuscular paralysis required ventilator/Ambu bag support in 3 (13%) low dose group and 6 (18%) patients high dose group. The hospital stay duration was 3.98 for the low dose group and 5.22 days for the high dose group. The mortality rate was 4% in the low dose group versus 6% in the high dose group. The manifestation of adverse effects of A.S.V. was also found to be significantly low in a low dose A.S.V. group.

Conclusion: we compared treatment outcomes and found low doses of A.S.V. may be utilized to optimize the effective dose and minimize its adverse effects. A beneficial trend for the low-dose group is seen.

KEYWORDS

Acute kidney injury(A.K.I.), anti-snake venom, neurotoxic, rural, vasculotoxic.

INTRODUCTION

Sneakbite is one of the significant health problems in India. Snakebite is a common occupational hazard of farmers and plantation workers generally from low socioeconomic status. World Health Organization (W.H.O.) had reported 1.2 million snakebite deaths (representing an average of 58,000 per year) from 2000 to 2019. Nearly half of the victims fall under the age-group of 30-69 and over a quarter being children under 15 [21]. The only specific antidote for snakebite is A.S.V. with or without adjunctive treatment in each case if needed. The correct/optimum dosage of anti-venom required for treatment is not clear.

The four "BIG" venomous snakes in India are the Indian cobra (*Naja naja*), Indian krait (*Bungarus caeruleus*), Russell's viper (*Daboia russelii*), and saw-scaled viper (*Echis carinatus*). The standard A.S.V. neutralizes the venom of these four big snakes. However, it is very difficult for an "on-duty" doctor to identify the particular snake species responsible for bites. Therefore, Polyvalent (polyspecific) anti-venoms are preferred in many countries which also include India. Moreover, the polyvalent drug is a good option. Polyvalent is almost as effective as monovalent. Further, some cross-neutralizing activity is recognized against the venoms of closely linked species. This provides an additional benefit when the species level identification is not possible. The polyvalent A.S.V. is effective against neurotoxic and vasculotoxic venoms. It is the mainstay of therapy, albeit expensive and scarcely available, especially in high-risk areas (P.H.C., C.H.C.) {full forms}

Although A.S.V. administration remains the mainstay of therapy, there is no unanimous accepted standard regimen regarding the optimum dose, frequency of administration, and duration of therapy. Ideally, the A.S.V. dose should be decided after measuring serial blood venom concentration. However, this is not clinically possible and practicable due to resource limitation and seriousness of the case. For example, the lethal dose is about 120 mg of cobra venom and 60 mg of krait venom. One mL of A.S.V. neutralizes 0.6 mg for cobra and 0.45 mg for krait bite. To decrease the fatality, the total observed dose of A.S.V. for a fatal cobra and krait bite should be 200 mL and 134 mL, respectively.

However, these snakes do not evenenom all the person with such a lethal dose. Currently, WHO has recommended and others have accepted that the initial dose of Indian polyvalent A.S.V. is 100 mL; that is, ten vials of polyvalent A.S.V. should be considered as the initial dose A.S.V. in all types of snakebite. It will neutralize 60 mg of Russell's viper venom and cobra venom; 45 mg of krait and saw-scaled viper venom will be useful in neutralizing significant venom amounts injected. A.S.V. Even though, it does not neutralize venom attached to receptors, it did so with circulating venom.

In the landmark report, Tarang et al. (1999) mentioned that the mean dose A.S.V. required to manage a case with envenomation effectively is 4.7 vials. Rashmi Ranjan et al. concluded in their systemic review that Low-dose A.S.V. is equivalent or maybe superior to high dose in the management of poisonous snakebites [14]. The low dose is also highly cost-effective as compared to the high dose [20]. Cherian et al. [JAPI 2013] reported less than 10 vial regimen is as efficient as high dose regime and has lesser adverse effects. It also lowers the cost of treatment as each vial of A.S.V. costs about 700 INR. Therefore, a reduction in requirement of 5-15 vials of A.S.V. reduces the cost of drug alone 3500 to 8000 INR. So low dose regime is expected to be beneficial in venomous snakebites without compromising morbidity and mortality. Additionally, it also provides cost-effective treatment.

Moreover, since A.S.V. is an animal serum product, some patients develop a hypersensitive reaction. Approximately, 20% of cases early (within a few hours) or late (5 days or more) following A.S.V. administration. A.S.V. causes severe adverse effects too and, at times, may confound the real cause of mortality in cases of snake bites. In this study, we tested for the effectiveness of A.S.V. in low (less than 10 vials) and high dosage (>10 vials). We also hypothesize that at the low dose the complication due to hypersensitivity will be low and hence the time of discharge will be less.

MATERIALS AND METHODS

A cross-sectional observational study was carried out in I.C.U./ emergency medicine of M.G.M. Medical College, Jamshedpur, Jharkhand, by scrutinizing the prescriptions of 70 snakebite cases

admitted to the I.C.U./emergency during the study period of 3 months from July to September 2020. All patients of snake bite admitted to medicine I.C.U./emergency of M.G.M. Medical College, Jamshedpur, were included in this study. Suspected snakebite cases or patients with unknown bites were excluded from the study. The preliminary data included age, gender, address, time, and bite site. We considered the diagnosis of vasculotoxic or neurotoxic, the two main types of snakebite. The diagnosis of the type of snakebite was made using clinical signs and symptoms. Patients with vasculotoxic snake bites presented bleeding from gums, gingival bleeding, epistaxis, prolonged bleeding from the bite site, hematuria, and extensive swelling. Those with neurotoxic bites presented with ptosis, blurring of vision, diplopia, type II respiratory failure (hypoxemia with hypercapnia), dribbling of saliva from the mouth's angle nasal twang, and giddiness.

Then we look for the dose and duration of A.S.V. administered. The dose and duration for which A.S.V. administration was determined. We discover Acute Kidney Injury (A.K.I.) due to snake venom, neuromuscular paralysis requiring ventilator support, hospital stay duration, and snake venom mortality.

Adverse effects reported to the A.S.V. were classified as early (anaphylactic, endotoxic, and pyrogenic) and late (serum sickness type) reactions. Not all signs and symptoms were apparent in every patient. Occasionally there was a clinical picture suggesting a combination of both vasculotoxic and neurotoxic snake bites. We analyzed data using descriptive statistics and Microsoft Excel. Statistical analysis was carried out using Fisher's Exact test.

RESULT

The prescriptions/BHT of 58 snakebite patients admitted to medicine I.C.U./emergency during the study period were scrutinized. The maximum number of patients admitted, 54 of the 58 (~93%), belonged to the rural areas in and around Jamshedpur, Jharkhand [Figure 1].

Figure 1 Residence-wise Distribution Of Snakebite Victims

Table 1 Gender-wise Distribution Of Snakebite Victim

	July 2020	August 2020	September 2020	Total
Males	5	17	8	30
Females	9	9	10	28
Total	14	26	18	58

Males 30 (52%) predominated the snakebite victims' list admitted while female 48% [Table 1]. Most snake bites, which is 74%, happened during the dark, as depicted in [Figure 2].

Figure 2 Monthly Analysis Of Time Of The Bite.

Lower limbs, mainly toes, and the ankle joint area were the most frequent snakebite site. 60% patients [n35] reported bite in Lower Limbs and 36% in Upper Limbs [n 21]. Only two cases of snakebite were found in the thoracic area. [Figure 3].

It was found the low dose of A.S.V. (≤ 10 vials) was used in 24 (41%) patients, and the high dose of A.S.V. (>10 vials) was used in 34 (59%) snakebite victim.

Patients receiving a low dose of A.S.V., 3 (13%) reported rash and itching on upper limbs immediately after administering the dose. In patients receiving a high dose of A.S.V., 5 (15%) suffered from ASV-

induced angioedema, and 6 (18%) patients reported fever, rigors, joint pain, and joint swelling. Thus, adverse effects were reported in three patients among those given a low dose of A.S.V. vis-à-vis 11 patients given a high dose of A.S.V. This decrease in the occurrence of adverse effects in patients receiving a low dose of A.S.V. was found to be statistically significant ($p = 0.033$, by Fisher's Exact test).

Figure 3 Analysis Of The Snakebite Site.

Duration of hospital stay was found to be relatively low (average 3.48 days) in patients given a low dose of A.S.V. as compared to those administered a high dose of A.S.V. (average 4.69 days). [Table 2].

Table 2 Parameters Of Patients With Snake Envenoming

A.S.V. used	No. of prescriptions	Outcome	Duration of hospital stay in days (average)	The occurrence of adverse effect (No. of patients)
For patients with neurotoxic signs and symptoms				
≤ 10 vials	12	Full Recovery	3.12	1 (8%)
>10 vials	18	Full Recovery	4.54	5 (28%)
For patients with vasculotoxic signs and symptoms				
≤ 10 vials	12	Full Recovery	3.84	2 (17%)
>10 vials	16	Full Recovery	4.85	6 (38%)

Table 3 Measurement Of Complications In Patients Given A Low Dose And A High Dose Of A.S.V.

	Acute kidney injury (A.K.I.) No. of patients	Neuromuscular paralysis requiring ventilator support (No. of patients)	Mortality
≤ 10 vials	5 (21%)	3 (13%)	1 (4%)
>10 vials	9 (26%)	6 (18%)	2 (6%)

Table 3 show a comparison related the outcomes of snakebite treatment in patients treated with low and high doses of A.S.V. The outcome shows that A.K.I. developed in a lesser number of patients [n 5 (21%)], getting a low dose of A.S.V. compared to those on a high dose of A.S.V. [n 9 (26%)]. This scenario was statistically insignificant ($p = 1$, by Fisher's Exact test). Out of 30 patients of neuromuscular paralysis, four (13%) patients were found to be receiving low dose A.S.V., and 6 (18%) patients receiving high dose A.S.V. developed severe hypoxia. They were put on an Ambu bag/ventilator.

The mortality rate of 4% was detected in patients who got low-dose A.S.V., and 6% in those who got high-dose A.S.V. was comparable ($p = 1$, by Fisher's Exact test). This was statistically insignificant again.

DISCUSSION

Our study report most patient belonging to rural areas of Jamshedpur with male/female victims are 52% and 48%. Moreover, most bites were reported in the lower limb as compared to other parts of the body. Regardless of the type of venom the time needed to recover was less when the patient was administered with low dosages of A.S.V. Furthermore, the chance of development of A.K.I. increase the dosage of A.S.V. All of the results align with other studies.

Cherian et al. (2013) reported that 70% of the victims were males (Bangalore)[5]. Rupal et al. from Mumbai reported that 82.8% of the victims are male, [13] so was reported from others. This difference is because females in the Jharkhand area also participate in an outdoor activity for day-to-day life. In our study, it is found that a low dose of A.S.V. (≤ 10 vials) has been used in 24 (41%) patients, while a high dose of A.S.V. (>10 vials), in 34 (59%) patients of snake bite. A.K.I. and neuromuscular paralysis needing ventilator support were observed and found to be less in patients who received a low dose of A.S.V. In high dose regimen, these outcomes are found to be more. This difference was statistically insignificant ($p = 1$, by Fisher's Exact Test), as shown in tables 2 and 3.

Tarang et al. (1999) also concluded no difference in the two groups' transfusion, dialysis, or ventilation requirements. [17] Srimannarayana et al. (2004) (12.9% patients on low dose suffered from A.K.I. vs. 25% patients on high dose suffering from A.K.I.) in Pondicherry in South India. [16] Another comparison seen in A.K.I. cases by Swapnil P Chube et al. in Maharastra is 20% in low dose regimen and 22.5% in high dose regimen. [15]

Paul et al. reported five deaths in the low-dose group giving a mortality rate of 10%, nine (18%) required dialysis, and three (6%) required ventilatory support. [11] There were seven deaths in the high-dose group giving a mortality rate of 14%, 13 (26%) required dialysis, and three (6%) required ventilatory support. The average hospital stay for the low-dose group was 8.42 days, while that of the high-dose group was 9.02 days.

Patients with neurotoxic paralysis needing a ventilator were 18% and 13% in high- and low-dose groups, respectively. Agarwal et al. [7] also showed no difference between lower doses of A.S.V. to higher doses in managing patients with severe neurotoxic variety. V paul et found 6% in both low and high dose group. [11]

In our study, the mean duration of hospital stay was a little less in patients given a low dose of A.S.V. compared to those given high dose A.S.V. This signifies similar rates of morbidity and mortality ($p = 1$) in both high- and low-dose groups, which again supports the benefits of using A.S.V. conservatively.

Cobra venom toxin acts mainly postsynaptically, whereas krait venom presynaptically. Most snakes get venoms containing both presynaptic and postsynaptic neurotoxins. A.S.V. is an antidote to snake venom and is effective against circulating venom. It has no action against the receptor site to which already venom get attached. A.S.V. neutralizes only circulating venom, A.S.V. has been used for many years. There is no consensus in most countries on the optimal dose and protocol of its administration. However, many studies have shown that treatment outcomes are comparable in patients receiving high doses and a low A.S.V dose.

Thomas et al. (1985) reported a higher number of patients [6 (22.2%)] developing A.K.I. in the low-dose group (average 7.9 vials) compared to 5 (19.2%) in the high-dose group (average 15.3 vials) with similar mortality rates in both the groups. [19] They cited a late presentation to the hospital for a higher number of cases developing A.K.I. even in the low-dose group.

Paul et al. (2004) reported a lesser number of patients developed A.K.I. in the low-dose group [9 (18%)] versus 13 (26%) in high dose group, and 3 (6%) patients required ventilator support in both groups. [11] This finding contracts Thomas et al. (1985)

Paul et al. further reported slightly lower mortality in the low-dose group than the high-dose group (10% vs. 14%). [11]

Recently Cherian et al., in their study, reported only a low dose of A.S.V. was used (6.7 ± 3.24 vials). [5] Among 54 patients, 12.9% of patients developed A.K.I., 12.9% of patients required ventilator support, and the mortality rate was 3.7%. Moreover, the cost of A.S.V. and its availability is a problem. Each 10 mL vial of A.S.V. in India costs between Rs. 500 to Rs. 800, and the use of lower doses of A.S.V. could translate into sizable savings to the patient and the community. Also, there is an increasing shortage of A.S.V. in several developing countries. Thus, it is imperative to evolve a regulated dosing protocol to overcome the crisis of availability of A.S.V. We did a comparative study as shown below.

Table 4 Comparative Studies Of Low A.S.V. Dosage

Investigator	Avg Dose of A.S.V. (Vials)	A.R.F. or dialysis (% of patients)	Ventilation (% of patients)	Adverse reaction to A.S.V. (% of patients)	Mortality (% of patients)
Tariang et al	4.7 ± 2.7	0%	3.4%	NA	0%
Srimannarayana et al	20.5 ± 4.3	50%	NA	16.67%	20%
Paul et al	6	18%	6	NA	10%
AM Cherian et al	6.7 ± 3.24	12.9%	12.9%	5.6%	3.7%

Swapnil P Chube	≤ 10	20%	13.3%	10%	3.3%
Our Study	≤ 10	21%	13%	12.5%	4%

Table 5 Comparative Studies Of High A.S.V. Dosage

Investigator	Avg Dose of A.S.V. (Vials)	A.R.F. or dialysis (% of patients)	Ventilation (% of patients)	Adverse reaction to A.S.V. (% of patients)	Mortality (% of patients)
Tariang et al	8.9 ± 3.5	0%	6.4%	NA	0%
Srimannarayana et al	37.6 ± 20.5	56.7%	NA	26.67%	30%
Paul et al	12	26%	6%	NA	14%
Swapnil P Chube	> 10	25%	15%	32.5%	5%
Our Study	> 10	26%	18%	32.4%	6%

Occasional reports of patients with severe snake envenomation recovering without the use of A.S.V. were also known. In our study, too, a low dose of A.S.V. was as effective as a high dose. However, a high dose was associated with more adverse outcomes.

The WHO says that the anti-venom reactions are dose-related. Our study also agrees with the WHO study findings, where patients receiving a high dose of A.S.V. developed significantly more adverse effects to A.S.V. ($p < 0.05$) compared to those receiving a low dose.

CONCLUSION

Our results align with previous studies that report low dosage (less than 10 vials) of A.S.V. have a better or least similar result that high dosage (more than 10 vials). A further advantage of the use of low dosage is the lesser risk of hypersensitivity development due side-effect of A.S.V.

Given that, medical expenditure is rising high day by day as a result economically backward people can not afford it. The government too needs a considerable fund to make it free to the hospital. Lastly, our country is facing an acute shortage of A.S.V. we need to optimize A.S.V. dosage. We need socio-cultural changes such as using footwear, no sleeping on the ground, not defecating in an open field, decreasing alcohol intake. These changes should become rituals. We need a robust national protocol for the diagnosis and treatment of snake venom. We expect low doses of A.S.V. can be utilized to be included in the protocol for the treatment of snakebite.

Finally, we would like to accept that the studies were done with a low sample size and we need to conduct similar studies for longer duration and larger spatial replicates.

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