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Postmarketing safety and usage study of anti-snake venom in a tertiary hospital in Talegaon, Maharashtra

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ABSTRACT

Aim

To study the adverse event profile and usage pattern of Anti Snake Venom (ASV).

Methods

This prospective observational study included 40 cases of snake bite admitted from July 2016 to December 2017. Adverse reactions to ASV were assessed. Clinical response parameters after ASV administration were also analyzed.

Results

24 cases had hemotoxic, 11 neurotoxic and 5 local envenomation. The mean number of vials used (19.35 +/- 12.89), time to control envenomation (22.4+/- 15.76 hours) and duration of hospital stay (4.9 +/-2.99 days) was not significantly different for any particular type of envenomation. They also did not vary between types of envenomation and whether bite to needle time was more or less than 6 hours. 27 adverse events were recorded in 9 patients. Most of these cases of early reactions were managed with antihistamines and corticosteroids. One case of possible anaphylaxis required vasopressors.

Conclusions

ASV of Premium Serums was well tolerated, and the number of adverse events were less than those reported in earlier studies. A mean of 19.35 vials were needed to control envenomation, an acceptable number based on WHO and National guidelines.

Keywords: Anti-Snake Venom Serum, Pharmacovigilance, Envenomation, Hemotoxic, Neurotoxic, Local

INTRODUCTION

There are about 300 species of snakes in India, 52 of which are poisonous. The big four namely common Cobra (*Naja naja*), Russell's Viper (*Dabiola russelii*), Saw-scaled Viper (*Echis carinatus*) and common Krait (*Bungarus caeruleus*) are highly venomous and believed to be responsible for most of the poisonous bites.[1] The only specific treatment available is a polyvalent Anti Snake Venom (ASV), effective against all four.[2]

ASV being of animal origin, can itself cause adverse reactions ranging from mild itching to fatal anaphylaxis. These patients have to be appropriately treated or given prophylactic premeditations. Usually more than 20% of cases will develop either early (within few hours) or late (5 days or more) allergic reactions following antivenom administration.[2]

Kalyan Kumar et al[3] mention that although the methodology of antivenom preparation has not advanced much since its discovery, procedures of purification and modes of utilization have changed considerably. Improved Purification of Antivenom by using Immunoglobulin fragments leads to increased tolerance, efficiency and safety of antivenom.

Premium Serums and Vaccines Pvt. Ltd (PSVPL) have recently introduced their brand of ASV manufactured to latest standards, at a dedicated facility. We conducted a Post Marketing Surveillance of this formulation in snake bite patients at Maharashtra Institute of Medical Education and Research (MIMER) Medical College, Talegaon, Pune. We also gathered information on the types of envenomation, total dose of ASV required and duration for recovery.

METHOD AND MATERIAL

This prospective observational study was carried out from July 2016 to December 2017 at MIMER Medical College, after approval by the institutional ethics committee. Every patient of either sex, with snake bite, and a clinical envenomation serious enough to administer ASV was enrolled after obtaining informed consent from the patient or his/her legally acceptable representative.

Patients were treated as per standard of care adopted at the institute. Pre-existing renal disease, uncontrolled chronic obstructive airway disease, congestive heart failure or previous myocardial infarction and consumption of diuretics, anticoagulants and antiplatelet drugs have been causes for exclusion in a few earlier studies as these illnesses and medications could have altered the clinical and laboratory profile of patients with envenomation.[4-6] This being a study in realtime patients were not excluded because of any comorbid conditions or concomitant medications. Pregnancy was also not an exclusion.

Patients were categorized as neuroparalytic envenomation if they presented with dysphonia, dyspnea, dysarthria, diplopia, ptosis, respiratory failure, head lag, associated hypertension and tachycardia. Patient presenting with signs of external and internal bleeding along with a WBCT >20 minutes were classified as hemotoxic envenomation. Local swelling, blistering, necrosis, pain at bite site, severe swelling, lymph node enlargement selected itself as local envenomation, as per the painful progressive swelling classification in Indian guidelines.[1]

PSVPL supplied ASV in 20 ml glass vials with 10 ml sterile water for injection, as diluent. 10 vials were administered by slow IV or infusion over one hour without pre-administration of antihistamines or corticosteroids.

Following an adverse reaction, ASV was discontinued. Hydrocortisone 100 mg IV and Inj. Pheniramine 0.5 mg/kg IV was administered. Once the patients had recovered, ASV was restarted slowly while closely observing the patient. Inj Adrenaline 0.1 ml of 1 in 1000 dilution administered subcutaneously when required. ASV was repeated based on the WBCT (Whole Blood Clotting Time). Antibiotics. Neostigmine, atropine, renal and ventilatory support treatment was administered as required. ASV was discontinued if 20 minutes WBCT showed clotting, patient had no further bleeding or spreading cellulitis and no evidence of evolving acute kidney injury in case of hemotoxic envenomation. In case of neurotoxic envenomation clinicians waited till ptosis had resolved, patient could speak adequately

Demographic information, type of the snake, time of snake bite, time interval between snake bite and ASV administration, total quantity of ASV given, laboratory investigations, comorbid conditions and concomitant medications was recorded on the case record form.

Results were analyzed using descriptive statistics, and parametric and non-parametric tests as appropriate

RESULTS

40 cases of snakebite were enrolled in the study. There were 26 males between 12 and 69 years (mean age 31.2 yrs.), and 14 females between 20 and 50 years (mean age 32.9 yrs). 20 were involved in agriculture, 11 were pursuing other professions while occupation was not recorded in 9 cases. At the time of bite, out of the 38 cases for whom information was available, 12 were walking, 21 working in the fields, 4 sleeping and 1 playing.

Distribution of types of envenomation was 24 hemotoxic, 11 neurotoxic and 5 local. (Table 1)

Table 1 Summary Table Showing Distribution of Envenomation, vs Mean Number of Vials Used, Time to Control Toxicity and Duration of Hospitalization

	Hemotoxic (n=24)	Neurotoxic (n=11)	Local (n= 5)	Total (n=40)	ANOVA (2 d.f.) Between Group (Not Significant)	
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*F*	*P*
No. of vials used	22.04 (13.11)	16.36 (11.80)	13 (12.55)	19.35 (12.89)	1.459	0.246
Time to stop ASV (hrs.)	24.46 (13.03)	21.18 (20.11)	15.2 (18.42)	22.4 (15.76)	0.750	0.479
Duration of hospitalization (days)	4.92 (2.99)	4.45 (2.43)	5.8 (4.55)	4.9 (2.99)	0.338	0.715

27 adverse events were recorded in 9 patients. Of these 4 cases had mild rigors and one had fever up to 102 degrees F. Three cases had permutations of nausea, vomiting, colic, tachycardia, itching and angioedema and all these cases of early reactions were managed with antihistamines and steroids. Only one case had hypotension sufficient to mandate the use of vasopressors, hence we could classify this as anaphylaxis. (Table 2).

Table 2 AEs Distribution in 9 Patients

Event	Mild	Moderate	Severe	Total
Rigors	4	0	0	4
Vomiting	3	1	0	4
Abdominal colic	1	1	0	2
Nausea	2	1	0	3
Itching	2	0	0	2
Urticaria	1	0	0	1
Fever	1	2	0	3
Tachycardia	4	0	0	4
Hypotension	1	1	0	2
Angioneurotic oedema	1	0	0	1
Anaphylaxis	1	0	0	1
Total	21	6	0	27

No patient required renal or respiratory support. When the number of patients suffering adverse events in different envenomation groups were compared, there was no significant difference. (Table 3).

Table 3 Number of Patients with ADRs vs Envenomation Types

	PRESENT	ABSENT	TOTAL
H	5 (20.8%)	19	**24**
N	3 (27.3%)	8	**11**
L	1 (20.0%)	4	**5**
TOTAL	**9 (22.5%)**	**28**	**40**

$\chi 2$=0.9049, 2 d.f., p=0.0705

The mean number of vials used, time to control envenomation and duration of hospital stay was not significantly different for any particular type of envenomation. 85% (34 patients) were controlled with 30 vials or less.

No difference was observed when the responses of cases were compared based on the latency to administer the first dose of ASV with a cut off of 6 hours (Table 4). The number of cases suffering adverse events also did not differ at this cut off (Table 5)

Table 4 Bite to Needle Time of Less Than or Greater Than 6 Hours vs Various Envenomation and Parameters

Envenomation Type		Time to ASV After Bite								
		Upto 6 Hrs.			More Than 6 Hrs.			Total		
		N	Mean	SD	N	Mean	SD	N	Mean	SD
No. of ASV Vials Used	Hemotoxic	18	23.00	14.24	6	19.17	9.70	24	22.04	13.16
	Neurotoxic	9	15.00	12.19	2	22.50	10.61	11	16.36	11.80
	Local Only	3	8.33	2.89	2	20.00	21.21	5	13.00	12.55
	Total	30	19.13	13.68	10	20.00	10.80	40	19.35	12.89
Duration of Hospitalization (Days)	Hemotoxic	18	5.22	3.17	6	4.00	2.10	24	4.92	2.95
	Neurotoxic	9	4.11	2.57	2	6.00	0.00	11	4.45	2.42
	Local Only	3	3.33	2.52	2	9.50	4.95	5	5.80	4.55
	Total	30	4.70	2.94	10	5.50	3.21	40	4.90	2.99
Duration of ASV Administration (Hrs.)	Hemotoxic	18	23.06	12.15	6	28.67	15.83	24	24.46	13.03
	Neurotoxic	9	19.33	19.97	2	29.50	26.16	11	21.18	20.11
	Local Only	3	7.33	2.31	2	27.00	29.70	5	15.20	18.42
	Total	30	20.37	14.81	10	28.50	17.72	40	22.40	15.76

ANOVA Table

Dependent Variable	Source	Type III SS	DF	Mean Square	F	P
No. of ASV Vials Used	Envenomation Type	185.20	2	92.60	0.55	0.58
	Time to ASV (6 hr)	141.07	1	141.07	0.84	0.37
	Envenomation Type*Time to ASV (6 hr)	310.41	2	155.20	0.93	0.41
Duration of Hospitalization (Days)	Envenomation Type	12.38	2	6.19	0.74	0.48
	Time to ASV (6 hr)	28.02	1	28.02	3.36	0.08
	Envenomation Type*Time to ASV (6 hr)	54.80	2	27.40	3.29	0.05
Duration of ASV Administration (Hrs)	Envenomation Type	287.22	2	143.61	0.57	0.57
	Time to ASV (6 hr)	753.79	1	753.79	3.01	0.09
	Envenomation Type*Time to ASV (6 hr)	190.40	2	95.20	0.38	0.69

Table 5 Bite to Needle Time of 6 hours vs Number of Patients Suffering Adverse Events

	Present	Absent	Total
Upto 6 hrs.	6	34	**40**
More than 6 hrs.	3	37	**40**
TOTAL	**9**	**31**	**40**

Chi sq=1.113, 1 df, p=0.117

DISCUSSION

Inspite of the massive public awareness campaigns it is still not possible to have the biting snake identified. This could be because some patients are bitten while sleeping, while other are either ignorant or too panicked to notice. Out of 40 cases, only in 9 cases was the snake identified. We had 2 cases each of cobra and krait bite and 5 with Russel's viper. Since the toxicity was as per the known information about the species, we can conclude that the identification was correct.

27 adverse events were recorded in 9 patients. (Table 3). All except one were considered early or pyrexial reactions and were managed by temporarily stopping ASV drip, administering a dose of hydrocortisone and starting the drip again. One case was classified as anaphylaxis since it presented with urticaria, tachycardia, hypotension and angioneurotic oedema. Vasopressors had to be administered to manage it. Incidence of adverse events in 22.5% patients is low as compared to many other studies.

Amin MR et al during their study in neurotoxic poisoning in Bangladesh, recorded anaphylaxis in 20 of 35 cases (57%). Patients had urticaria, itching, nausea vomiting, wheezing and rhonchi. Although they labelled these symptoms as anaphylaxis, only 2 cases had to be administered adrenaline. The rest were managed by steroids, very much like us.[4]

Seneviratne SL et al,[7] in Srilanka, reported that acute adverse reactions to AVS occurred in 102 (55.4%) cases and this did not differ whether or not premedication was administered. Fan HW et al [5] in Brazil reported ADRs in 25 of 101 cases administered ASV, a number closer to ours

In India Deshmukh VS et al,[8] in their study on 50 cases, reported adverse reactions in 62% i.e. 31 cases. There were 51 events reported of which 27 (53.94%) were of early anaphylactic type and 23 (45.1%) were pyrogenic in nature

Deshpande RP et al[9] studied 2 snakebite seasons. Out of 164 patients who received ASV, 92 (56%) experienced adverse events. The most common reactions were chills, rigors (69.3%) followed by nausea and vomiting (41.3%). 15% patients suffered from moderate to severe reactions like hypotension and sudden respiratory arrest. There was a higher incidence of antivenom reactions in cases of haemotoxic snake bites (52.17%) as compared to neuroparalytic presentations (21.74%) unlike our findings where the distribution of cases with adverse events were not significant across envenomation types (table 3)

Some studies mention the number of vials used to control envenomation. Suchithra N et al[6] mention that median number of vials used to control envenomation was 22 with a range of 3 to 62 vials. Bhattacharya P[10] in his series of 13 neuroparalytic cases needed between 10 and 30 vials over two days. Amin Mr et al[4] used 10 vials per patient for neurotoxic poisoning.

In addition to observing adverse reactions to ASV we also kept a record of number of vials used in various types of envenomation, the duration of hospital stay, time to control envenomation and bite to needle time.

The mean of 19.35 vials of ASV were utilized, the distribution being hemotoxic envenomation 22.04+/- 13.16, neurotoxic 16.36 +/-11.8 and local 13 +/- 12.55. The difference was not statistically significant. This is within the parameters suggested in both WHO guidelines as well as Indian guidelines for management of snakebite.[1,2] In fact 85% cases were controlled with less than 30 vials

The time necessary to note clinically acceptable improvement and to stop ASV did not vary depending upon the type of envenomation (table 1).

National guidelines[1] mention that if one waits for 6 hours for manifestations to develop it would result in systemic envenoming and high fatality. Suchithra N[6] also noticed that those patients who had a bite to needle time of greater than 6 hours has a higher incidence of complications. This could translate into a longer hospital stay, a greater number of vials used and longer time to stop ASV.

With this in mind we decided to divide the population into those who received the first dose of ASV within 6 hours of bite and those who received it later. We did not find any difference (Table 4) in the mean number of vials used, mean duration of hospital stay or duration to control envenomation, possibly because our study was underpowered. But if one looks at the trends, one finds that for neurotoxic and local envenomation number of vials, hospital stay and time to stop ASV were higher if bite to needle time was >6 hours. This was not so in case of hemotoxic envenomation. This may be because the hemotoxic cases show obvious signs of bleeding and WBCT changes. These acute findings are quickly managed resulting in faster recovery and discharge. The number of cases experiencing adverse events in the before and after 6 hours group were also not different.

CONCLUSION

ASV manufactured by PSVPL manifested expected side effects, which were less than reported in earlier studies. It was found to be effective requiring an average 19.35 vials per treatment irrespective of the envenomation syndrome.

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