Original Article

Post Marketing evaluation of Anti Snake Venom (ASV) administered as a standard treatment for snakebite. Experience from western India

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Abstract

Aim: To study the safety profile and effectiveness of Anti Snake venom (ASV) in western India

Methods: This retrospective study gathered safety, and clinicoepidemiologicaldata on 157 patients admitted at Shri Sainath Hospital, Dharampur, Gujarat, from July 2022 to February 2023.

Results: Majority were bitten between August and November**.** There were 88 males, 5 to70 yrs. (mean 39.14), 69 females, 2 to 70 years (mean 40.32). 6 of these were children ranging from 2 to 12 years.134 were agricultural labourers.

120 cases were analysable. 17 had neurotoxicity and 103 had haemotoxicity. Mean (SD) number of vials used was 10.1(6.2), time to discontinue ASV was 3.0(5.2) hours, and duration of hospital stay was 4.5(2.6) days. Patients bitten by saw scaled vipers were discharged early. In Russel's Viper bites, number of vials used, was higher if the bite to needle time was less than 6 hours

9 patients suffered 24 adverse events, with two possible cases of anaphylaxis. One case had urticaria, itching and tachycardia as a triad. The remaining were isolated events of mild urticaria, itching, tachycardia, hypotension, cough, rigor.

Conclusion: 10.1 vials were needed on average for control of envenomation with no fatalities or severe comorbidities. Adverse events were reported in 5.7% cases. The ASV brand used was well tolerated. Patients who were brought late suffered more renal complications

Key words: Anti-Snake Venom Serum, Adverse events, Envenomation, Hemotoxic, Neurotoxic

Introduction

Snakes have been feared, loathed, and worshiped in India. Cobras are considered sacred both by Hindus and Buddhists. Millions living in villagesface severe morbidity and mortality due to snakebite. WHO estimates that India has close to 50000 deaths per year due to snakebites [1]

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Anti Snake Venom (ASV) is a life saver but being of equine origin, it is likely to cause adverse events ranging from mild itching, fever chills to fatal anaphylaxis. These can be prevented by using appropriate premedication, ormust be managed post hoc. Following ASV administration, more than 20% patients will suffer from early (within few hours) or late (5 days or more) allergic reactions. [2]

ASV has been available in India for about 100 years and the method of preparing antivenom has not changed much. However improved purification of antivenom and use of immunoglobulin fragments has led to increased tolerance, efficacy, and safety.[3]

Shree Sainath Hospital, Dharampur, Gujarat, is a major centre for snake bite management, and are using ASV manufactured by Premium Serums and Vaccines Pvt. Ltd (PSVPL) since the past few years. We conducted this retrospective study as part of a post marketing surveillance program for the PSVPL formulation. We also gathered information on the types of envenomation, total dose of ASV required and duration for recovery

Materials and Methods

Shree Sainath Hospital, Dharampur, has been treating snakebite for about 30 years. The local government recognises their effort and supplies them with free ASV every year.

In this retrospective evaluation we have gathered data from July 2022 to February 2023 during which predominant supply was of ASV manufactured by PSVPL. After reviewing data from the hospital pharmacy, we could isolate 157 cases where PSVPL product was used. The snake had been identified based on charts, photographs taken by the patient or relatives, dead snake being presented and based on symptomatology.

Patients who presented with ptosis, dysphonia, dyspnoea, dysarthria, diplopia, respiratory failure and head lag were categorised as neurotoxic envenomation. This was further confirmed if he/she was not able tocount to 30 in a single breath.

Epistaxis, bleeding gums, vomiting, haematemesis, haemoptysis, bleeding from freshly healed wounds, acute abdominal pain along with a (Whole Blood Clotting Time) WBCT >20 minutes indicated hemotoxic envenomation.

Up to 10 vials of PSVPL ASV were administered by slow IV or infusion. Pretreatment with hydrocortisone IV is a practice in this hospital. Following an adverse reaction ASV, was discontinued. An additional dose of Hydrocortisone 100 mg iv and Pheniramine maleate 0.5mg/kg were administered and on recovery, slow IV was attempted again.

In case of haemotoxic envenomation, when the WBCT had normalised, and there was no further bleeding, ASV was discontinued. In case of Cobra bites, resolution of ptosis, ability to speak full sentences or count to 30 in a single breath were indicators for stopping ASV. In case of Krait bites the team did not exceed the ten vials given initially. Antibiotics, neostigmine with atropine, renal and ventilatory support were given as necessary.

We gathered data on adverse events, demographics, concomitant medications and morbidities, total amount of ASV used, duration of hospital stays, bite to needle time on a case record form

Analysis of data

Any patient who had received even one does of Premium ASV was included in the adverse event dataset. Hence all 157 cases were considered for evaluation of adverse events. There were about 37 patients who had been administered ASV by local doctors before admission. In most cases 1 or 2 vials had been administered but that made calculation of bite to needle time difficult. Hence all these cases were deleted from analysis and we had a final dataset of only 120 cases

We created an Excel master sheet and analysis was carried out using descriptive statistics, and parametric and non-parametric tests as appropriate

Results

157cases were divided into 88 males, 5 to 70 yrs. (mean 39.14yrs.), 69 females ,2to70 years (mean 40.32 yrs.), including 6 children ranging from 2 to 12 years. 134 were agricultural labourers. Data about the distribution of snake types, the type of residence and the place of bite, and method of identification of the

snakes, and consciousness of patient on admission is mentioned in table1. Tourniquet was used in only 33% cases and 17% were immobilised. Month wise pattern of bites is shown in Figure1. There were 24 adverse events in 9 patients. (Table 2).

Table 1: Other relevant information based on type of snake (n=157)

	Saw-scaled Viper (n=21)	Russels Viper (n=110)	Cobra (n=6)	Krait (n=20)	Total (n=157)
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Place of bite					
Inside house	2 (9.5%)	2 (1.8%)	0 (0.0%)	18 (90.0%)	22 (14.0%)
In the farm	13 (61.9%)	88 (80.0%)	2 (33.3%)	1 (5.0%)	104 (66.2%)
Outside/around house	6 (28.6%)	20 (18.2%)	4 (66.7%)	1 (5.0%)	31 (19.7%)
Type of residence					
RCC construction	4 (19.0%)	18 (16.4%)	0 (0.0%)	3 (15.0%)	25 (15.9%)
Semi build house	5 (23.8%)	26 (23.6%)	3 (50.0%)	5 (25.0%)	39 (24.8%)
Thatched house	12 (57.1%)	66 (60.0%)	3 (50.0%)	12 (60.0%)	93 (59.2%)
Identification of snake					
Dead snake	0 (0.0%)	10 (9.1%)	1 (16.7%)	0 (0.0%)	11 (7.0%)
ID from chart	18 (85.7%)	95 (86.4%)	5 (83.3%)	19 (95.0%)	137 (87.3%)
Live snake	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Photo of snake	3 (14.3%)	4 (3.6%)	0 (0.0%)	1 (5.0%)	8 (5.1%)
Was patient conscious on admission					
Yes	20 (95.2%)	109 (99.1%)	6 (100.0%)	17 (85.0%)	152 (96.8%)
No	1 (4.8%)	1 (0.9%)	0 (0.0%)	3 (15.0%)	5 (3.2%)
Total	21 (100.0%)	110 (100.0%)	6 (100.0%)	20 (100%)	157 (100.0%)

Table 2: Adverse Event distribution in 9 patients (n= 157)

Events	Mild	Moderate	Severe	Total
Urticaria	3	1	1	5
Itching	4	1	0	5
Tachycardia	4	0	1	5
Cough	1	0	0	1
Hypotension	1	0	1	2
Bronchospasm	0	0	0	0
Angioneurotic oedema	1	0	0	1
Anaphylaxis	2	0	0	2
Fever	0	1	0	1
Chills	0	0	0	0
Rigors	2	0	0	2
Late serum sickness type reaction	0	0	0	0
Total	18	3	3	24

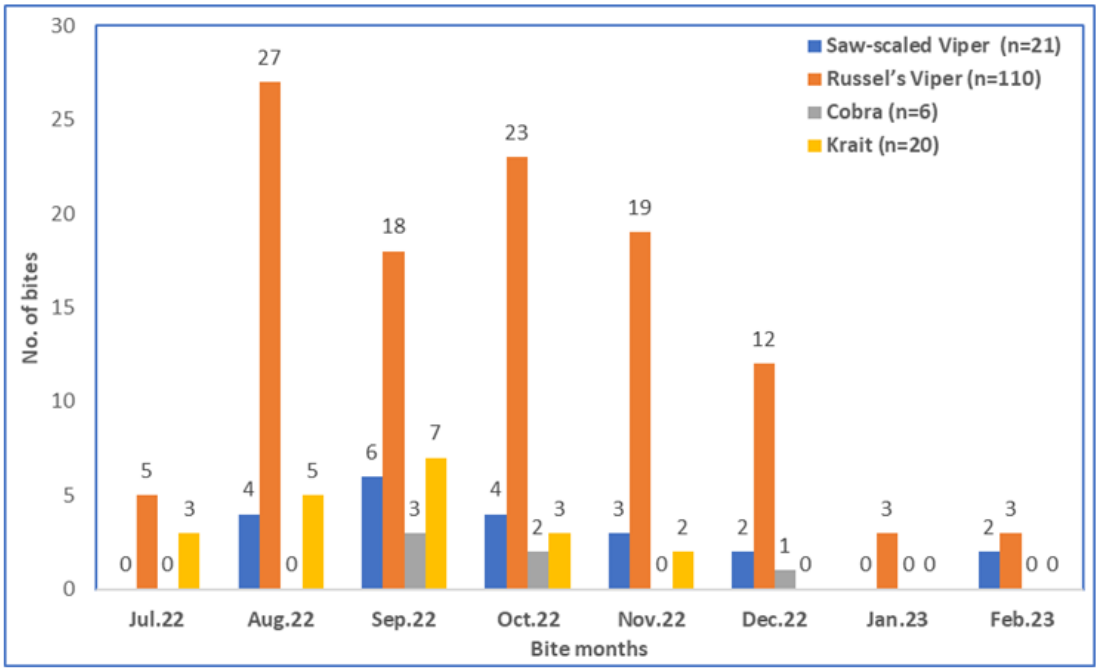

Fig 1: No. of bites per month with snake type (n=157)

For analysis of number of vials used, duration to stop ASV and hospital stay all patients who had received ASV outside the hospital were disregarded and only 120 cases were analysed. This is summarised in table4. In case of saw scaled vipers a significantly less vials were used, for a shorter period, with fewer days of hospitalisation. The mean number of vials used across all snake types was 10.1, cobras and Kraits needing a mean of 10 vials, Russel's Viper 11.2 and saw scaled viper only 5.1.

The mean starting dose for any envenomation was around 5, max was 10 vials, the most used dose being 5 vials. (Table 5)

Table 4: Mean Number of vials used, duration of hospital stay, duration of ASV administration distributed by snake type (n=120) ANOVA

	N	Number of vials used Mean (SD)	Time to stop ASV Hours Mean (SD)	Hospitalisation Days Mean (SD)
Cobra	3	10.0 (0.0)	0.3 (0.2)	4.0 (1.0)
Common Krait	14	10.0 (0.0)	3.3 (6.7)	5.3 (2.5)
Russel's Viper	84	11.2 (6.9)	3.5 (5.4)	4.7 (2.8)
Saw Scaled viper	19	5.1 (2.4)	1.1 (2.9)	2.9 (0.9)
Total- Mean (SD)	120	10.1 (6.2)	3.0 (5.2)	4.5 (2.6)
F value		5.499	1.435	0.236
P value		0.001	2.904	0.038

Table 5: Distribution of doses across recovery

No. of vials	N	Mean	SD	Median	Mode	Min	Max
First dose	120	5.53	1.87	5.00	5.00	3	10
Second dose	69	5.19	1.06	5.00	5.00	3	10
Third dose	22	5.59	2.40	5.00	5.00	3	15
Fourth dose	7	7.86	3.93	5.00	5.00	5	15

Discussion

Most snakebites occur during the monsoons. (Figure 1) Due to flooding, snakes leave their habitat and forage out. Their prey like rodents come close to human settlements in search of food. Cobras come close to the dwellings in search of prey like rodents, hence many cobra bites happen around the house. Kraits on the other hand, enter the house in search of warmth and end up biting individuals in their sleep, [2,4] A look at table1 indicates that majority of Krait bites happened inside the house (90%), while 4 of 6 cobra bites happened around the house. Interestingly, 15% bites occurred in houses with RCC (Reinforced Cement Concrete) construction. We have noticed that snakes can easily enter ground floors of RCC houses.

There were 3 cases brought unconscious to the Hospital, all of which were bitten by a Krait. Majority krait bites happened indoors, in thatched or semi built houses allowing access to the snake, and the bite was on the limbs, one on the ear and 3 on torso.

All the offending snakes were identified; 137 from charts, 8 had photographed the snake themselves, 11 brought dead snakes and one even brought a live one.

There were 24 adverse events (AEs) in 9 patients (Table 2). Interestingly, two cases of anaphylaxis accounted for 13 of these 24 events. These cases had been administered ASV outside the hospital and arrived with signs of anaphylaxis which had to be managed with adrenaline, steroids, and antihistamines. But based on the possibility that the ASV administered outside the hospital could have been manufactured by PSVPL, we have included the cases in the compilation. The remaining events were generally mild in nature. Only one case had the triad of urticaria, itching tachycardia a classic sign of early reaction. The rest were isolated cases of tachycardia, itching, hypotension, urticaria. There were no reports of late serum reactions.

A method of grading anaphylaxis based on clinical symptoms was suggested by Brown Simon. [5] Based on those criteria, case # 120 which had severe urticaria, tachycardia and hypotension, mild itching and cough, along with moderate grade of rigors with fever could be classified as moderate since there was no hypoxia or neurological signs as proposed in the article. Case # 150 experienced moderate urticaria and itching accompanied by mild tachycardia and rigor. This could be classified as mild.

Incidence of adverse events is significantly lower that any of the earlier studies. AEs in earlier studies ranged from >50% in past studies [8,9,10,11] to 16 and 22% in recent studies. [12,13,14]

In Sri Lanka Seneviratne SL et al [6]reported 102 (55.4%) adverse events in patients administered ASV. Prior use of prophylactics did not affect the rate of reaction. Fan HW et al [7] from Brazil, concurred. They recorded adverse events in 25 of 101 cases inspite of using promethazine as premedication.

In our study hydrocortisone was used as prophylactic but going by above findings we can assume that this was not the reason behind fewerad verse effects. Better manufacturing techniques as proposed by Kalyankumar et al,[3] could be an explanation.

Detailed analysis on 120 cases who received only PSVPL ASV is presented in table 4.

The mean number of vials used to control envenomation was 10 with Cobra and Common Krait, Russel's Viper 11.2and saw scaled vipers needing 5.1 vials. These numbers are lower than the Indian national guidelines [15]. Other investigators have also used less vials than the recommendations but more than us. Our numbers are close to others for neurotoxic bites but lesser for haemotoxicbites. [8,12,13,14] We would attribute this to the clinical experience gathered over the years, and due to mass awareness program undertaken which helped in patients reaching hospitals much earlier without wasting time.

We also compared the time to stop ASV administration and days of hospitalisation between various snake types (table4). It was noted that Russsel's viper bite cases stay longer, though this trend did not reach significance. Sudeepkumar et al [14] and Ramesh J et al [13]were also faced with similar nonconclusive results.

Suchitra N et al [16] used a 6-hour cut off and concluded that a bite to needle time of greater than 6 hours leads to a higher incidence of complications We found a significant difference for number of vials used,(Tables 6) but not in case of hospital stay.

Table 6: Number of vials used for various snake types against bite to needle time

	Up to 6 hrs.			More than 6 hrs.			Total		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Snake type									
Cobra	2	10.00	-	1	10.00	-	3	10.00	-
Common Krait	10	10.00	-	4	10.00	0.00	14	10.00	-
Russel's Viper	64	11.56	5.83	20	10.00	9.60	84	11.19	6.88
Saw-scaled Viper	13	4.92	2.50	6	5.50	2.35	19	5.11	2.40
Total	89	10.38	5.54	31	9.13	7.91	120	10.06	6.22
ANOVA table									
Source	**Type-III SS**		**df**	**Mean square**		**F**		**'p'**	
Snake type	403.212		3	134.404		3.767		0.013	
Total no. of vials	0.450		1	0.450		0.013		0.911	
Snake type*Total no. of vials	18.465		3	6.155		0.173		0.915	
Corrected Total	4608.592		119						

Russel's viper bite required more vials if patient was brought to hospital early. Similar trend was observed by Sudeepkumar et al [12] for haemotoxic envenomation. The possible explanation for this could be that haemotoxicity manifests as overt symptoms that must be aggressively treated leading to higher use of ASV. Another thought is that delay results in the venom reaching the tissue compartment, and some of it being metabolised leading to a smaller number of vials being required.[17]

We follow the syndromic approach. We estimated the required number of vials based on clinical condition and experience and administered them in one go. The preferred dose for any iteration was 5 vials, although a few cases needed 10 vials (Table 5). We did not wait for the 6-hour WBCT and completed the total ASV administration in less than 6 hours. This is a unique method of administration. There is some logic in doing this as suggested by Sanhajaria S et al[17] and Blessman J et al [18]in their review of snake venom pharmacokinetics. Based on this thought, a patient who comes soon after the bite require higher doses, due to higher amount of venom available for neutralisation, giving results as above.

Since statistics did not show correlation between bite to needle time and morbidity, we decided to study outliers. The mean hospital stay was 4.5 +/- 2.6 days. Table 7 below is a study of those who stayed for 11 days or more. This supports the finding by Suchithra N et al[16] that delay in use of ASV will lead to higher renal complications

Table 7: A study of outliers in hospital stay

Patient #	Hospital stay in days	Bite to needle in hours	Envenomation	# of vials of ASV used	Venom related complications
1	13	10	Haemotoxic	45	Haemodyalisis [HD] 8 times
64	14	14	Haemotoxic	20	Forced Alkaline Dialysis and HD
94	12	4	Neurotoxic	10	Ventilator
109	11	1	Haemotoxic	15	Haemodyalisis
125	19	7	Haemotoxic	15	Haemodyalisis
129	11	4	Neurotoxic	11	Ventilator, 52 hours

WHO has published a draft guideline [19], about the Target Product Profiles for performance of a polyvalent ASV used in south Asia. It recommends a minimal and an optimal target to achieve, optimal being exactly half of minimal. Performance of PSVPL ASV is better than optimal in this study

Table 8: Performance of ASV as per Target Product Profile

Optimal performance criteria	Study finding
Case Fatality Rate CFR < 1%	No fatality
Amputations < 1%	No amputations
Persistence of coagulopathy at 24 hours post ASV administration < 3%	We meet this criteria, since ASV administration was stopped within 7 hours
Progression to Acute kidney Injury (AKI) post ASV is < 5 %	Only 3 of 120 cases needed dialysis. 2.5%
Need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofing of blisters) < 5%	2 cases required incision and drainage required

Conclusion

In this series of cases only 5.7% patients experienced adverse events which could be managed clinically. A mean of 10.1 vials were required to control envenomation. ASV manufactured by PSVPL is well tolerated, safe and effective. Russel's vipers bites required more vials if patient was brought to hospital early. Patients who were brought late suffered more renal complications

Ethical Clearance/Statement of Ethics: Shree Sainath hospital ethics committee Registration# ECR/1846/lnst/GJ/2023 Project approval dated 8th September 2023

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