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## The Pattern of Usage of ASV in Snake Bite Cases



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### ABSTRACT

**INTRODUCTION:** Snakebite is a commonly occurring occupational hazard to the people involved mainly in the agricultural sector in tropical and sub-tropical areas.. Anti-snake venom (ASV) is the only evident treatment option for snake bite envenomation. In India, poly valent anti-venom is the effective antidote against the Big4 category. That includes Common Cobra, Russell's viper, Saw-scaled viper and Common Krait. **MATERIALS AND METHODS:** This was a Multicentre retrospective observational study. The study was conducted in selected four hospitals in central Kerala. The study was done for duration of 10 months. All victims of poisonous snake bites admitted in the general medicine department of the above four hospitals from January 2017 to December 2017 was taken for the study. Average number of ASV vials used was compared with respect to different hospitals, different types of snakes and severity of bite. **RESULTS:** In order to study these treatments we classified these based on the number of ASV vials used. The use of 10+10+10 regimen is seen commonly seen in krait bite. While comparing the variations of ASV regimens according to severity of bite, it were classified as mild, moderate and severe cases based on the severity of bite. In case of mild cases the medium number of vials used was 20 vials, and for moderate cases 15 vials. The severe cases requires 25 vials of ASV. But the minimum vial usage is least for severe cases. The usage of ASV in different hospitals also compared in this study. **CONCLUSION:** There were 22 different regimens used for administering the ASV in snakebite species. The predictability in the regimen had very weak correlation with the severity scale of snakebite or any other presenting feature. Majority of these regimens did not adhere to any standard treatment guidelines. **SIGNIFICANCE:** Study shows the need of local treatment protocol.

## INTRODUCTION

Snakebite is a commonly occurring occupational hazard to the people involved mainly in the agricultural sector in tropical and sub-tropical areas. With deforestation and urbanization snakebite has become an important public health problem to the society<sup>1</sup>. The occurrence of snake bite is very common in countries with heavy rainfall and humid climate<sup>2</sup>.

India is the leading nation to have the highest snake bite mortality when compared to other nations in the world<sup>3</sup>. According to world estimate around 5 million people are affected by snakebite and about 100,000 death occurs annually<sup>5</sup>. WHO included snake bite in the list of Neglected Tropical Disease in early 2009<sup>1</sup>. The conventional use of harmful first aid practices like the use of tourniquets or cutting the wounded area and sucking the venom makes further complications that lead to worsening the condition of the patient. Most of the mortality are due to seeking conventional treatment methods rather than reaching the hospitals with provisions of definitive treatment. There are about three major families of venomous snakes in India; these include Elapidae which covers cobra, king cobra, krait and coral snakes, the Viperidae family consisting of Russell's viper, saw-scaled viper, humpnosed pitviper, Malabar pitviper, green pitviper and Russell's viper of croatalinae subfamily and the Hydrophidae family comprising these snakes<sup>7</sup>. Among these species there are four major poisonous snakes namely, Common Cobra (*Naja naja*), Russell's viper (*Daboia russelii*), Saw-scaled viper (*Echiscarinatus*) and Common Krait (*Bungarus caeruleus*) these contribute to the venomous bites in India. The non-venomous snake bites do not harm the patient apart from causing a panic reaction or a local injury to the patient<sup>3</sup>. The non-venomous snake bites do not harm the patient apart from causing a panic reaction or a local injury to the patient<sup>3</sup>.

Anti-snake venom (ASV) is the only evident treatment option for snake bite envenomation. In India, poly valent anti-venom is the effective antidote against the Big4 category. That includes Common Cobra, Russell's viper, Saw-scaled viper and Common Krait<sup>3</sup>. Antivenom is produced by injecting small doses of snake venom into horse body to produce an immune response. Antibodies produced due to these immune response are collected from the animal body. This is used as anti-snake venom<sup>8</sup>. ASV is manufactured in liquid and

lyophilised form. Liquid form can be stored upto 2years whereas lyophilized form can be for 5 years and must be kept in cool temperature<sup>3</sup>.

Two methods of administration

1. Intravenous push injection: Both liquid and lyophilised form can be given by slow intravenous injection (not more than 2ml/min). The advantage of this method is that it is economical and the early reaction due to ASV can be observed earlier.
2. Intravenous infusion: Both freeze-dried and liquid ASV can be used. The ASV is diluted in 5-10ml of isotonic fluid per kg body weight, ie250-500ml of isotonic saline or 5% dextrose and is infused over one hour at constant rate.
3. Intramuscular injection of Antivenom: This method is only adopted in certain conditions like when intravenous route is impossible, as a first aid measure in primary care centres to avoid the lapse before seeking medical attention in hospitals specialised for snakebites.

The Indian polyvalent anti-snake venom is effective against the 4 snake types which is included in the Big4 category i.e., Common Cobra, Russell's viper, Saw-scaled viper and Common krait. The neutralizing capacity of anti-snake venom depends upon the amount of venom produced by each snake types. About 1ml of Indian polyvalent ASV can neutralize about 0.6mg of Cobra and Russell's viper venom and about 0.45mg of krait and saw-scaled viper<sup>12</sup>.

## MATERIALS AND METHODS

This was a Multicentre retrospective observational study. The study was conducted in selected four hospitals in central Kerala. The study was done for duration of 10 months. All victims of poisonous snake bites admitted in the general medicine department of the above four hospitals from January 2017 to December 2017 was taken for the study. The inclusion criteria include those admitted with poisonous snake bite and treated with anti-snake venom. Patients below 12years of age, Victims admitted with non-venomous snake bites and those with incomplete case records were excluded from the study. Data was obtained from the medical records which include admission sheets, patient history notes, patient treatment charts, laboratory data reports, progress sheets, discharge summary, nurses' records, prescriptions, doctor's order, daily admission list maintained by Medical Records Department (MRD),

statistics maintained by the ICU of general medicine department of the four selected hospitals. In order to record necessary data from the sources mentioned above, case record form (CRF) was designed based on the data required for the study. CRF contains patient demographic details like age, sex, hospital, snake type, patient complaints on admission, vital signs (respiratory rate, blood pressure, heart rate), respiratory parameters like pulse oximetry, biochemical test results, microbiological reports (gram stain and culture sensitivity reports), snakebite treatment –ASV its dose, route and duration, dose and duration of antibiotics and the list of medications used to treat anaphylaxis and clinical outcome.

Average number of ASV vials used was compared with respect to different hospitals, different types of snakes and severity of bite.

Multiple linear regression analysis was used to analyse the predictability of number of ASV vials needed, infusion rate of ASV, infusion time of ASV with respect to epidemiology, laboratory parameters and symptoms.

The ASV usage patterns are also tested for its adherence with the standard protocol and the reason for the deviation is depicted as bar diagram based on their percentage distribution in each hospitals.

The regimens of ASV vials were coded and rank assigned accordingly. The median of these ranks distributed were tested for their statistical significance with respect to type of snake bite, hospitals and severity of bite using Kruskal Wallis rank test.

## RESULT

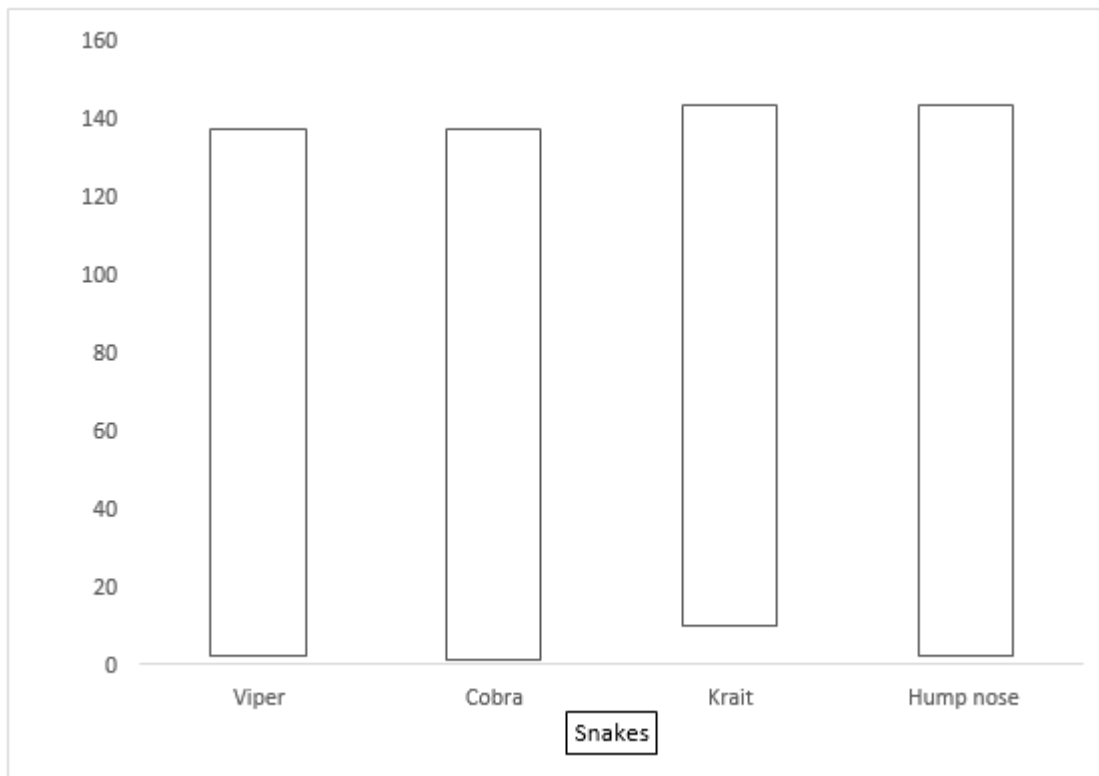
In our study a total of 144 poisonous snake's bites were reported in the four selected hospitals during our study period. We collected 15 cases from hospital 1, 34 cases from hospital 2, 43 patients from hospital 3 and 51 patients from hospital 4. In hemotoxic envenomation cases due to the lack of data in the case records, we couldn't differentiate between Russell's viper and Saw-scaled viper. Hence we considered hemotoxic envenomation cases as viper cases in common.

The regimens of ASV vials were coded and rank assigned accordingly. The median of these ranks distributed were tested for their statistical significance with respect to type of snake bite, hospitals and severity of bite using Kruskal Wallis rank test. ASV vial use regimen in

snake bite victims as shown in Table:1

**Table No. 1: Different ASV regimens in different hospitals.**

Regimens	ASV vial	Time of infusion (mint) 1 <sup>st</sup> dose	Time of infusion (mint) 2 <sup>nd</sup> dose	Time of infusion (mint) 3 <sup>rd</sup> dose	No. Of dosing
Regimen 1	2	5			1
Regimen 2	5	59.5±69.03			1
Regimen 3	8	60±42.42			1
Regimen 4	10	68.27±50.56			1
Regimen 5	15	55±12.24			1
Regimen 6	20	80±43.204			1
Regimen 7	30	300±			1
Regimen 8	5+5	59.5±69.03	240±11.09		2
Regimen 9	5+10	330±42.42	230±175		2
Regimen 10	5+15	165±190.9	120±0		2
Regimen 11	8+2	300±0	300±0		2
Regimen 12	8+10	60±0	60±0		2
Regimen 13	8+4	145±.122.5	180±0		2
Regimen 14	10+5	132.7±107.34	145±118.75		2
Regimen 15	10+10	120±0	139.6±106.6		2
Regimen 16	10+20	210±127.2	210±121.2		2
Regimen 17	10+15	72.5±102.5	120±0		2
Regimen 18	15+5	60±0	77.5±102.53		2
Regimen 19	15+10	60±0	60±0		2
Regimen 20	20+10	60±0	97±111.5		2
Regimen 21	20+5	50±14.1	112.5±125.7		2
Regimen 22	10+10+10	280±108.4	95±101.14	223.3±144.5	3



**Figure: 1** comparative study to analyse the variation of ASV regimen in different type snakes

The graph shows that the most areas lie on the regions were maximum number of vials. Here we gave rank for different ASV regimens. Each regimen corresponds to the particular number of vials of ASV. In order to analyse the difference in median of the rank of ASV regimens in each snake Kruskal Wallis test following chi square distribution.

**Table No. 2: Rank distribution of ASV regimen in snakes**

Rank	Viper	Cobra	Krait	Hump nose
Minimum rank	2	1	10	2
1 <sup>st</sup> quintile	10	10	10	10
Median	79.5	10	58	68
2 <sup>nd</sup> quintile	96	61	129	96
Maximum	137	137	143	143

From table 3 there is statistically significant difference in the median of the rank of ASV regimens used, in short the ASV vial usage regimen is found to be different for different snake.

**Table No. 3: Rank distribution of ASV regimen in snakes**

Test performed	Degrees of freedom	P value ( CHI distribution )
Kruskal Wallis test following chi square distribution	3	0.003

Figure 2 shows the rank of ASV used in mild moderate and severe cases.

In order to analyze the difference in median of the rank of ASV regimens in each severity scale Kruskal Wallis test following chi square distribution (table 4).

**Table No. 4: Rank distribution according to severity of bite**

Rank	Mild	Moderate	Severity
Minimum rank	1	2	77
1 <sup>st</sup> quartile	10	20.5	122.5
Median	52	80	126.5
2 <sup>nd</sup> quintile	80	96	129
Maximum	143	143	137

Figure 3 shows the variation of ASVregimens in different hospitals. In order to analyse the difference in median of the rank of ASV regimens in each hospital Kruskal Wallis test following chi square distribution (table 6).

**Table No. 5: Rank distribution for ASV regimen according to bite severity**

Test	Degree of freedom	P value(Chi distribution)
Kruskalwallis test following chi square distribution	2	0.000197

**Table No. 6: The rank distribution of ASV regimens for different hospitals**

Rank	Hospital 1	Hospital 2	Hospital 3	Hospital 4
Minimum rank	2	2	10	1
1 <sup>st</sup> quintile	64	10	10	10
Median	76	10	52	80
2 <sup>nd</sup> quintile	88	92	96	96
Maximum	143	125	129	137

From table7 there is statistically significant difference in the median of the rank of ASV regimens used in hospital, in short the ASV vial usage regimen is found to be different for hospital.

**Table No. 7: The rank distribution of ASV regimens for different hospitals**

Test	Degrees of freedom	P value ( Chi distribution )
Kruskal Wallis test following chi square distribution	3	0.00

## DISCUSSION

Reduced availability of sufficient quantity of ASV as a main reason to reduce the success of snake bite treatment. To reduce the risk and wastage and to improve the effectiveness the following must practice.

- Determine envenomation
- Appropriate initial dose
- Need of repeated dose
- Endpoints for ASV therapy

The impact of developing a local protocol is considerable in this study. The reduction of vials may reduce overall economic burden. 1

In this study it is identified that different treatment regimens of ASV used in different



hospitals. In order to study these treatments we classified these based on the number of ASV vials used. Based on these regimens number, the regimens can be ranked, each rank corresponds to the specific regimen and analysed with different factors using Kruskalwallis test following chi square distribution. In general, the null hypothesis is that there is no median rank difference between the factors compare. The result of study shows relation to the results obtained by Ghosh et al.

The study compares the variations of ASV regimens in different type of snakes. In case of viper bite the median rank of 79.5 shows 8+4 vials. In cobra biter cases median shows 10 vials of ASV, and for krait was 20vials. In hump nosed pit viper cases it was 10 vials. The maximum vial usage seen in case of krait bite. The use of 10+10+10 regimen is seen commonly seen in krait bite, this can be because of the uncontrolled symptoms even after the initial doses of ASV. The factor can be because of the low sensitivity of ASV or non-effectiveness ASV that lead to this higher amount of ASV use. These patterns of ASV use is not recommended in the standard as it exceeds the recommended doses of ASV. The result of this study was contrary to the study by Paul et al, that the hemotoxic viper envenomation requires higher dose of ASV. But the result of this study shows similarity to the result of study by Tariang et al.

While comparing the variations of ASV regimens according to severity of bite, it were classified as mild, moderate and severe cases based on the severity of bite. In case of mild cases the medium number of vials used was 20 vials, and for moderate cases 15 vials. The severe cases requires 25 vials of ASV. Although there is median difference between ASV regimens used in different severity scale. The significant fact is that the maximum ASV regimen use has higher in mild and moderate when compared to maximum ASV regimen in severe envenomation scale is less. This paves light to the argument of the researchers that low dose ASV regimens are enough to treat envenomation even in the high profiled envenomation. The result of this study is contrary to the guidelines for the management of snake bites.

The study assessed the ASV regimens in different hospitals. Hospital 4 uses 2 vials of ASV as the minimum vial usage and hospital 3 uses 10 vials. The maximum vial usage was 30 vials in most of the hospitals (hospital 1, 3,4). The average vial usage was highest for hospital 3 (20 vials), followed by hospital 4 (15 vials). This is significant to prove that the variations in the ASV regimens are dependent on a higher degree on hospitals compared to snakes.

Hence either this result is proving the fact that there is higher requirement of a local treatment protocol and strong recommendations has to be made in order to follow the standard guidelines in these hospitals.

## CONCLUSION

There were 22 different regimens used for administering the ASV in snakebite species. The predictability in the regimen had very weak correlation with the severity scale of snakebite or any other presenting feature. Majority of these regimens did not adhere to any standard treatment guidelines. The number of ASV vials administered also showed a positive correlation with the incidence of renal failure. The high variation in the pattern of ASV administration in a small geographical area included in the study points to the relevance of locally developed treatment protocol.

## CLINICAL SIGNIFICANCE

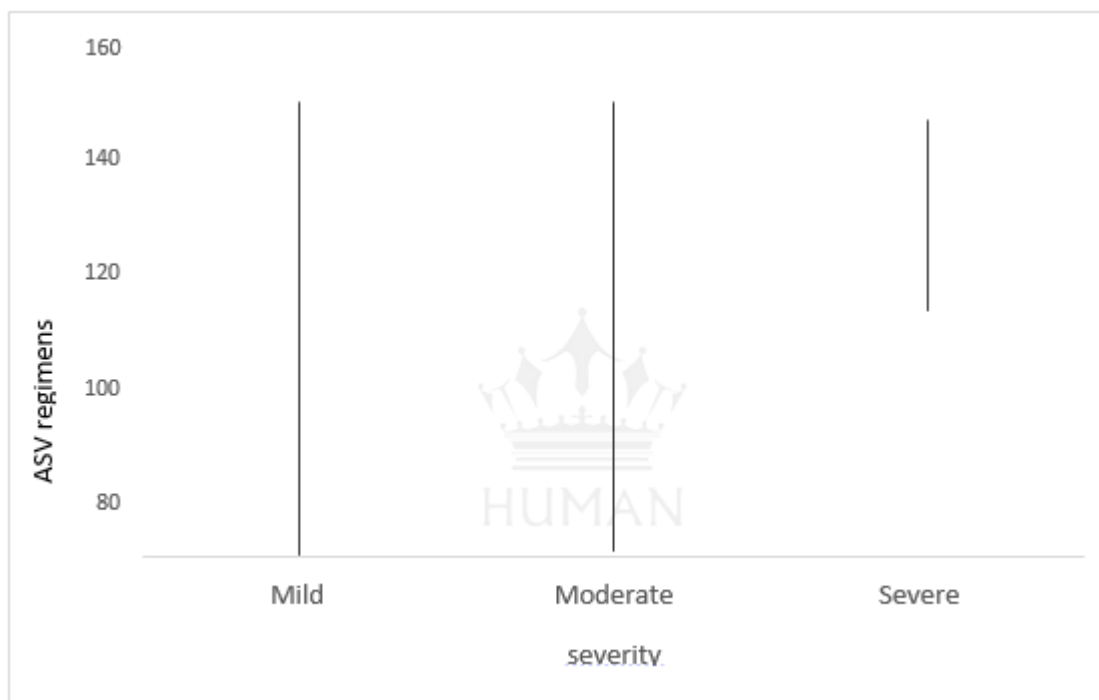
The study found different regimens of ASV and found the ASV vials usage trend in different hospitals this lightens to the need of local protocol for the management of snakebite cases.

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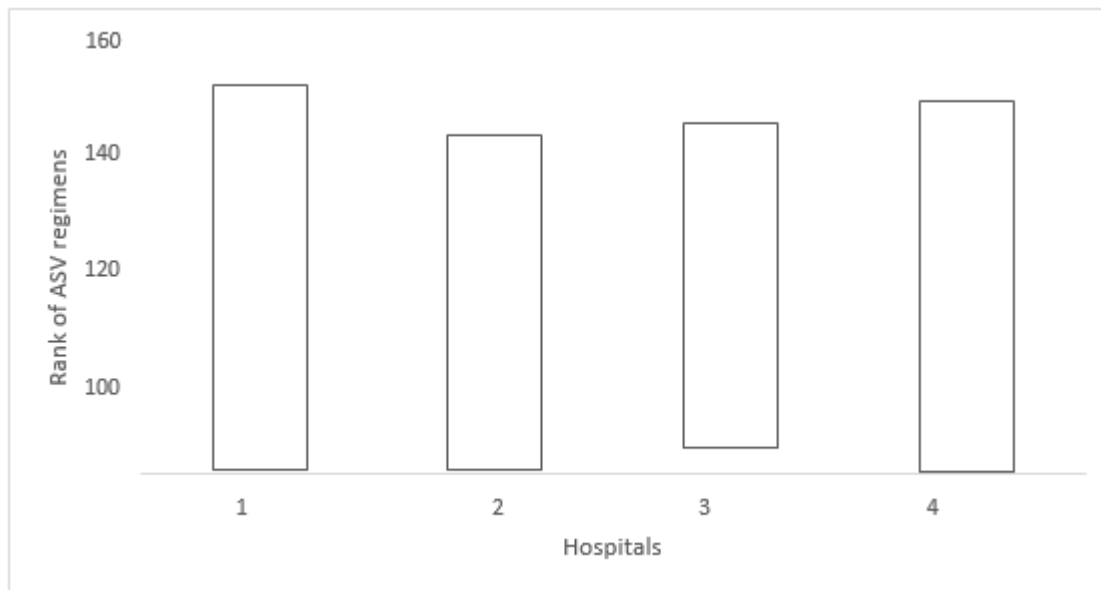
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## TABLES AND FIGURES



**Figure No. 2: COMPARITIVE STUDY TO ANALYSE THE VARIATION OF ASV REGIMEN ACCORDING TO SEVERITY OF BITE**



**Figure No. 3: COMPARITIVE STUDY TO ANALYSE THE VARIATION OF ASV REGIMEN IN DIFFERENT HOSPITALS**

<i>Image</i>	<b><i>Dona Johnson</i></b> <i>Nirmala College of Pharmacy Muvattupuzha</i>
<i>Image</i>	<b><i>Aby Paul</i></b> <i>Nirmala College of Pharmacy Muvattupuzha</i>
<i>Image</i>	<b><i>Swapna Saju</i></b> <i>Nirmala College of Pharmacy Muvattupuzha</i>
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