Rational Use of Anti-Snake Venom: Trial of Various Use Regimes in Hemtoxic Snake Envenomation

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Abstract

Background: India is estimated to have the highest snakebite mortality in the world. The hitch with determining the optimum ASV dose is that the quantity of venom injected at a bite is very variable. There are very few studies to determine the effective dose of ASV. But recent studies have found that low dose ASV is as good as or even better (lesser complications) than high dose ASV. Despite evidence for smaller doses from evidence-based medicine, most centers are still using large doses. The is a need for investigating in this area to know the effective dose of ASV in management of snake bite patients resulted in taking up of present study. *Material and Methods:* this study carried out in Medicine department, SIMS, Shimoga for 6 months from January 2017 to June 2017. 100 snakebite patients with haemostatic abnormality admitted to Mc Gann Hospital. A detailed history was taken in all the patients and a through physical examination was done. CBC, RFT, LFT, BT,CT, PT, INR, ECG, is done. The two study groups are 50 consecutive patients formed Group I (Conventional high dose regime (100ml) group). 50 consecutive patients formed Group II (Low dose regimen (30ml) group). *Results:* The mean age was 37.67 (± 4.56) years. With male to female ratio being 1.3:1. The mean Snakebite to ASV given time was 14.5hours. Average CT (at presentation), Group 1- 22.6±7.59 mins. Group 2- 29.47 ±5.59 mins. ASV dose required, Group 1- 325 ±183 ml. Group 2-175.75 ±±87.4 ml. Time lapse for CT normalization, Group 1- 24.97±5.58 hrs. Group 2- 14.93±4.49 hrs. About 20-25% of patients developed acute renal failure [11 (22%) and 5 (10%) patients in groups I and II respectively]. Number of patients died in Group 1-5 (10%). Group 2-4 (8%). *Conclusion*: The observation that very low dose of ASV is adequate to save lives of victims of poisonous snake bites with early hospitalization and good supportive management. This will definitely decreases economic burden on the society.

Keywords: Venom; Snakebite.

Introduction

India is a country known to the western population as a country of snake charmers. India is estimated to have the highest snakebite mortality in the world.

Snakebite is a major problem in rural India with more than 2 lakh snakebites being reported in India annually of which 35,000-50,000 die [1-2]. A nationally representative study of 123,000 deaths from 6,671 randomly selected areas in 2001–03 conducted by Mohapatra B et. al. revealed an annual age-standardized rate of 4.1/100,000. This proportion represents about 45,900 annual snakebite deaths nationally (99% CI 40,900 to 50,900) [3].

The estimated death in India is 50,000/yr, an underestimate because of lack of proper registration of snake bite. Most of the fatalities are due to the victim not reaching the hospital in time where definite treatment can be administered. In addition community

is also not well informed about the occupational risks and simple measures which can prevent the bite. It continues to adopt harmful first aid practices such as tourniquets, cutting and suction, etc. Studies reveal that primary care doctors do not treat snakebite patients mainly due to lack of confidence [4]. At the secondary and tertiary care level, multiple protocols are being followed for polyvalent anti-snake venom (ASV) administration, predominantly based on western textbooks.

The hitch with determining the optimum ASV dose is that the quantity of venom injected at a bite is very variable, depending on the species and size of the snake, the mechanical efficiency of the bite, whether one or two fangs penetrated the skin and whether there were repeated strikes. A proportion of bites by venomous snakes do not result in the injection of sufficient venom to cause clinical effects [5]. About 50% of bites by Malayan pit vipers and Russell's vipers, 30% of bites by cobras and 5-10% of bites by saw-scaled vipers do not result in any symptoms or signs of envenoming [6]. Also, neutralization by antivenom must occur almost immediately after venom enters the circulation to significantly impact on recovery time of the coagulopathy due to envenomation [7].

ASV used in India is polyvalent and contains antivenin against cobra, Russell's viper, krait, saw scaled viper. Each vial of ASV containing 10 ml of antivenin costs about 500 rupees. To the rural poor patients from agricultural background who are the most common victims of snake bite it is a huge burden. Another problem with ASV is that, it being a animal serum product some patients develops hypersensitivity reactions to it.

The infrastructure of the medical profession in India is mal-distributed in such a manner that it is very difficult to protect this poor rural population against the snake bite. Scientifically and ethically we, the doctors can not treat the patients of snake bite properly.

In response, Government of India, Health and Family Welfare Department has prepared a National Snakebite Management Protocol [8] to provide doctors and lay people with the best possible, evidence-based approach to deal with this problem in country.

There are very few studies to determine the effective dose of ASV. Previously many tens of vials of ASV were used in the treatment of snake bite- sometimes being given direct IV. But recent studies have found that low dose ASV is as good as or even better (lesser complications) than high dose ASV [9-12]. Despite evidence for smaller doses from evidence-based

medicine, most centers are still using large doses.

The is a need for investigating in this area to know the effective dose of ASV in management of snake bite patients resulted in taking up of present study.

Materials and Methods

This study was carried out in Mc Gann Hospital, Shimoga. The material of study consisted of 100 consecutive patients of snakebite patients with haemostatic abnormality admitted to Mc Gann Hospital from January 2017 to June 2017 over 6 months.

A Prospective study consisting of 100 snakebite patients with haemostatic abnormality was undertaken to study the efficacy of low dose anti snake venom over conventional regimen in the treatment of patients with poisonous snake bites.

Inclusion Criteria

A total of 100 snakebite patients with haemostatic abnormality presented to our hospital between January 2017 and June 2017, of patients who were aged ≥ 15 yrs with history of snakebite within the previous 24 hrs and had signs and symptoms of systemic envenomation which included hemostatic abnormalities in the form of spontaneous GI bleeding, uncontrolled bleeding from external wounds, prolonged CT (>10 min), PT (INR>1.5), aPTT (> 2x control), shock (requiring ionotropic support), cardiac arrhythmia, abnormal ECG, Acute renal failure evidenced by oliguria, anuria, rising creatinine (>1.5 mg/dl), albuminuria, hemoglobinuria / myoglobinuria, dark brown urine were found eligible for the study

Patient allocation: There are four medical units in our hospital. Two Units A and B were chosen for trial of high and low-dose regimes. The two study groups, as follows, were formed.

50 consecutive patients formed Group I (Conventional high dose regime group).

50 consecutive patients formed Group II (Low dose regimen group).

ASV was administered as mentioned in Table 3. Groups I and II received regimens I and II respectively.

Patients with ARF were managed with fluid challenge and hemodialysis, wherever indicated.

The study was approved by the Institute Ethics Committee and informed consent was obtained from each patient.

Exclusion Criteria

1. No signs of envenomation
2. No signs of haemostatic abnormality
3. Known cardiac, hepatic and renal disorder
4. Presentation after 24hrs

A detailed history was taken in all the patients and a through physical examination was done as per the proforma.

Investigations are as Follows

- Blood routine (Hemoglobin percentage, Total count, differential count, Erythrocyte sedimentation rate).
- Bleeding time, clotting time repeated at intervals
- PT, APTT and INR
- Random blood sugar (Fasting blood sugar/Post prandial blood sugar was done whenever necessary), blood urea, serum creatinine.
- Urine routine analysis (Sugar, Albumin and microscopy)
- ECG

Special Investigations

a. Chest X-ray / screening (whenever required)
b. Serum electrolytes (whenever required)

Statistical Analysis

Observations

100 consecutive patients of snake bite with haemostatic abnormality admitted to Mc Gann Hospital, Shimoga from January 2017 to June 2017 were studied. They were given treatment according to Regimen I-50 patients, Regimen II-50 Patients. The following are the observations made from this study.

Age Distribution

The mean age of the studied patients was 36±5 years and 39±6 years in groups I and II respectively. Most of the patients were males and were agricultural laborers. All our patients were from rural areas. Approximately 40% had the bite on one of the lower limbs, 30% had bite in upper limbs.

Table 1: Showing age distribution

Age group (in years)	Regimen I (50) No. of patients (Percentage)	Regimen II (50) No. of patients (Percentage)
Less than 30	4(8)	3(6)
31-40	20(40)	18(36)
41-50	12(24)	13(26)
51-60	5(10)	4(8)
61-70	4(8)	4(8)
71-80	3(6)	5(10)
More than 81	2(4)	3(6)
Total	50(100)	50(100)

Table 2: Showing Sex distribution

Sex	Regimen I (50) No. of patients (Percentage)	Regimen II (50) No. of patients (Percentage)
Male	33(66)	35(70)
Female	17(34)	15(30)

Table 3: Different regimens of ASV used in the study

Regimens	Loading Dose	Followed By	End-Point
Regimen I (Conventional High Dose Regimen)	100 ml	50 ml Q 6 Hours Till CT normalizes	Till CT normalizes
Regimen II (Low Dose Regimen)	30 ml	30 ml infusion over 6 hours process repeated till CT normal, followed by 30 ml over 24 hours	Till 24 hours after CT normalizes

Table 4: ASV Therapy

Risk Factors	Regime I		Regime II	
Average CT (at presentation)	22.6 ±7.59mins		29.47 ±5.59mins.	
ASV dose required	325 ± 183 ml		175.75 ± 87.4 ml	
Adverse reaction	12(24%)		15 (30%)	
Time taken for CT normalization	24.97 ±5.58 hrs		14.93 ± 4.49 hrs	
Recurrence	8 (16%)		6 (12%)	
Outcome	Cured	Death	Cured	Death
	45(90%)	5(10%)	46 (92%)	4 (8%)

Table 5: Characteristics of patients with mild envenomation (clotting time 11-20 min) and severe envenomation (clotting time >20 min)

|	Mild envenomation		Severe envenomation	
	Regimen I	Regimen II	Regimen I	Regimen II
No. of patients	30	32	20	18
Snake Bite to ASV given time (hours)	13.2±12.2 hours	14.9±13.44 hours	10.55±13.67 hours	13.5±11.46 hours
Mean CT (min)	15.48 ± 5.3	17.33 ± 3.2	24±5.56	27±5.47
Average dose of ASV (ml)	267±65.5 ml	154±74.8 ml	394±58.9 ml	235±94.9 ml
Time taken to CT normalization(hours)	14.56±5.5	11.76±2.4	22.76±5.7	16.67±5.8
Relapse of bleeding after treatment	7	2	5	3
No. with ARF	4	1	7	4
No. with DIC	5	4	8	7
Duration of stay (days)	5	4	8	7
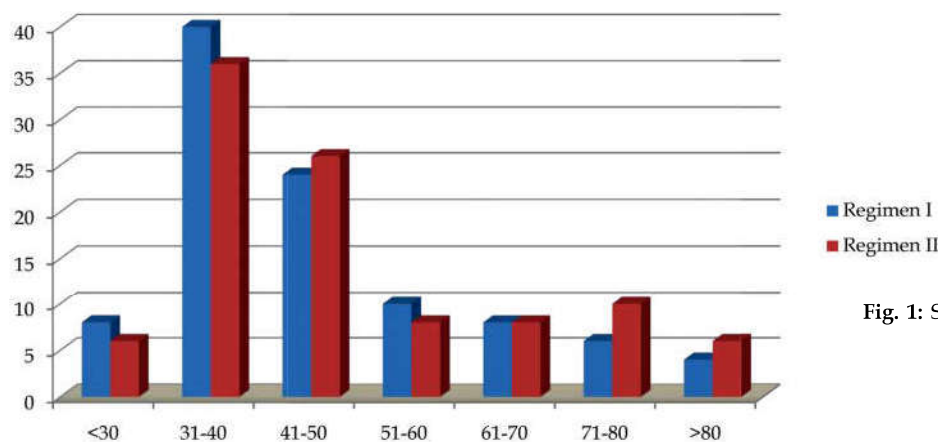
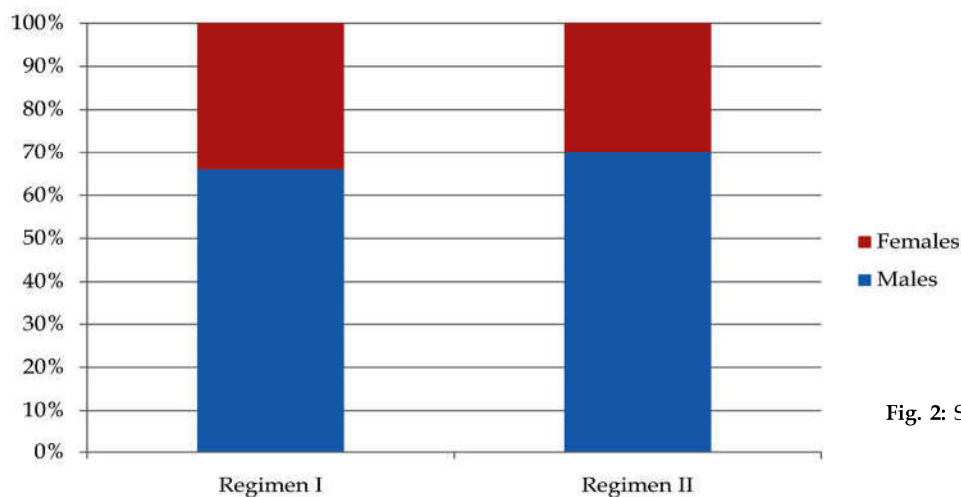Fig. 1: Showing age distribution

Fig. 2: Showing Sex distribution

The male to female ratio was 1.3:1. More number of males are affected by snake bite in our study compared to females.

The average requirement of ASV, time lapse for CT norormalization, incidence of adverse reaction and recurrence of coagulation dysfunction in various groups are shown in below table.

Most of patients had local swelling (swelling at the site of bite). 55% patients had presented with signs of mild envenomation, whereas 45% patients presented with signs of severe envenomation (incoagulable blood).

Adverse ASV reactions were mainly in form of itching, urticaria, and erythema; and responded to antihistaminics and hydrocortisone. Ten patients, however, developed hypotension and required adrenaline.

Characteristics of patients with mild and severe envenomation are shown elaborately in Table

The mean Snake bite to ASV given time was 14.5hours; only one-third of patients presented within six hours of bite. The mean bite to needle time was 13.2 hours and 14.9 hours in groups I and II respectively. 30% and 36% of patients in groups I and II respectively reached the hospital after 24 hours of snakebite.

About 20-25% of patients developed acute renal failure [11 (22%) and 5 (10%) patients in groups I and II respectively].

Of the total of 100 patients enrolled in the study, 9 (18%) patients succumbed to various complications. causes contributing to death were DIC, ARF and septicemia.

Discussion

The study is aimed at knowing usefulness of lower dose regiment over conventional regimen of ASV.

The observations made in 100 case of snake bite with haemostatic abnormality admitted to the Mc Gann Hospital Shimoga from January 2017 to June 2017 are discussed here and the results have been compared with other studies.

Age

The age of patients in this study ranged from 25 years to 89 years with maximum number of patients in the age group 31 to 40 years (38%). Mean age 37.67(± 4.56) years. This is consistent with findings of

AM Cherian et al [13] where Mean age was 35.72± 14.42years.

In most of the Indian studies commonly affected patients are rurual agricultural laboures it is consistent with our study (AM Cherian et al [13], J Srimannarayana et al [10]).

Sex

There were 68 males (68%) and 32 females (32%) in the present study. The male to female ratio was 1.3:1. This findings is consistent with that of AM Cherian et al [13] – males 70%), females (30%); V Paul et al [9] - 75% male, 25% female.

The mean bite to needle time of our patients was 14.5 hours; only 38% of patients presented within six hours after bite. This was in contrast to the studies by Thomas et al [14] and Tariang et al [15]. Where majority of patients reached hospital within six hours. This explains higher requirement of ASV in the current study; experimentally delay in administering antivenom results in steep increase of median effective neutralizing dose [16]. Further, none of the patients in Tariang's study [15] groups had incoagulable blood; whereas almost 60% of our patients had incoagulable blood at presentation, thus requiring more of ASV.

In a study by Paul V et al [9], authors found no additional advantage of giving fixed 12 vials (120 ml) of ASV over six vials (60 ml) of ASV. However all the cases included in that study were those who arrived within 24 hours of bite, whereas 36 (66%) of our patients arrived after 24 hours of bite. However, ours being a tertiary referral center, we had a higher load of critically ill patients and thus had higher mean requirement of ASV.

However, the average dose of ASV required in Regimens II in our study was significantly lower than that required in Regimen I. The lower requirement in regimens II was probably due to the delivery of ASV by continuous infusion and thus more accurate titration of dose, as opposed to delivery by multiple bolus doses in Regimen I.

Repeated high doses of ASV to restore the clotting time to normal do not seem to be necessary to reduce the mortality and a smaller dose sufficient to bring down the clotting time seems to be adequate. As evidenced in this study. The body's detoxifying system will bring down the clotting time eventually though it may take a slightly longer time.

In patients with *mild envenomation*, Regimen II was found as effective as the other regimens and at the

Table 6: Average dose of ASV and modes of administration in various studies

Study	Protocol	ASV Required
Our Study	Regimen I (Conventional High Dose Regimen)	325 ± 183 ml
	Regimen II (Low Dose Regimen)	175.75 ± 87.4 ml
Vijeth et al (2000), Pondicherry[17]	Intermittent bolus doses:	
	Initial - 100 ml	179.2 ml
	Repeat - 50 ml q 6 hr till CT corrects to normal	
Thomas and Jacob (1985), Kerala[14]	Traditional schedule:	153 ml
	40 ml in 1st hour, 40 ml in next 2 hrs, 40 ml in next 3 hrs, 30 ml every 3 hours.	
	Modified Schedule:	79ml
	20 ml in 1st hour, 20 ml over 2 hrs,20 ml every 3 hrs till CT normalizes.	
	(After CT normalizes, 20 ml in 5% dextrose over 24 hours).	
Tariang et al(1999), Vellore[15]	Continuous iv infusion:	
	High dose:	89 ml
	20 ml in 100 ml 5% dextrose over 1 hr, followed by 20 ml in 100 ml 5% dextrose over 4 hrs, till CT normalizes, and then, 2 vials	
	over 24 hours	47ml
	Low dose:	
	20 ml over 1 hour, followed by 10 ml in 100 ml of 5% dextrose over 4 hours till	
	CT normalizes, then 10 ml in 100 ml 5% dextrose over 24 hours.	
J Srimannarayana et al[10]	Conventional High Dose Regimen) 100 ml	376 ± 205.83 ml
	(Low Dose Regimen) 30ml	197.67 ± 76.4 ml
Paul V et al[9]	High dose group	120 ml
	Low dose group	60 ml

same time it had comparatively lesser requirement of ASV at 154±74.8 ml.

In patients with *severe envenomation*, Regimen II with requirement of ASV at 235±94.9 ml, where as Regimen I which required 394±58.9 ml. Regimen II appear to be significantly economical regimens as compared to Regimen I (standard regimen).

Following these new regimens, the amount of ASV saved with Regimen II in our study was as much as 100 ml to 200 ml in mild and severe envenomation. Further, giving extra dose of ASV after CT normalization reduced recurrence of coagulation dysfunction. In the low-dose group there were five deaths giving a mortality rate of 8%, which is consistent with study by V Paul et al [9] which showed mortality of 10%.

Following the prescribed regimes suggested in this study, the requirement of ASV will become automatically low in mild and severe envenomation, even though the mean requirement of ASV may be high due to more number of severe envenomation cases, as in this study. May be due to late presentation or referral of cases to our tertiary hospital.

The mean dose requirement in mild and severe cases with the prescribed regimes concluded from this study was found to be not much different from that required by Bhat RN et al [18] study, Slightly higher mean dose requirement in mild and moderate envenomation in our study was due to extra dose of ASV given after

correction of CT. this is recommend to prevent relapse of coagulation dysfunction. Since there are several studies reporting the recurrence of coagulation defect as a significant problem [17,19,20].

Since more than 8 years, there has been a growing scarcity of ASV due to various reasons (including animal rights protests and introduction of Drug price control by Govt of India) and there are periods when ASV is not available at all in the market. In the government sector, there are often logistic difficulties in procuring ASV due to stringent tender and quotation rules or shortage of funds.

However, because of the high cost and limited availability of ASV and reports of patients with severe envenomation recovering without its use, there was a change in dosage protocols from high to low. The antivenin is effective only if given early enough to neutralize the venom in the circulation, Therefore, the use of large doses late in the course is unlikely to be effective [21].

Conclusion

The observation that very low dose of ASV adequate to save lives of victims of poisonous snake bites with early hospitalization and good supportive management. It is of very much importance in developing countries like India. While there was no

additional advantage in following a high-dose regime for snake bite cases, there was considerable financial gain by following the low-dose regime. It is a win-win situation for both patients and the institution/nation.

Acknowledgement

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