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Research Article

Effect of low dose ASV with supportive care in poisonous snake bites in Marathwada region, Aurangabad, Maharashtra, India

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ABSTRACT

Background: Due to a large number of patients and severe scarcity of ASV with patches of unavailability and unaffordable high cost, low doses of ASV had to be compulsorily used for treatment of poisonous snakebites. The main objective is to study the effectiveness of low dose ASV (total <50 ml) in the management of poisonous snake bites in the scenario of global ASV scarcity.
Methods: Patients of snake bites with signs of envenomation were included in this observational, prospective study. Immediately, low dose (30 to 50 ml) of ASV was started after carefully testing intravenously. The patients were kept under intensive observation with supportive management (artificial ventilation, neostigmine-atropine, blood and fresh frozen plasma, as needed).
Results: In the study of 309 patients, slight male preponderance was seen (161 males and 148 females).144 patients had vasculotoxic, 122 patients had neurotoxic and 43 patients had mixed type (both vasculotoxic and neurotoxic) of envenomation. Average dose of ASV given was 35.30 ml. 297 patients survived, 12 died. In 42 cases having both neurological and vasculotoxic (mixed) snake bite, 7 patients (16.66%) died. Among 122 neuroparalytic cases, 5 (4.0983%) died. We did not get any mortality in the 145 cases of vasculotoxic snake bites. There was no statistically significant difference in the outcome of the patients whether they received higher or low doses of ASV.
Conclusions: There was no significant difference in the outcome of poisonous snake bites whether low dose (<50 ml) or high doses (>50 ml) of ASV were given and practically all the victims who came on time, survived with low doses of ASV. This is very important in developing countries like India where there is high incidence of poisonous snake bites and scarcity of ASV.

Keywords: Low dose ASV (anti-snake venom), Vasculotoxic, Neuroparalytic, HBD, VAP

INTRODUCTION

The present study was conducted from May 2013 to Oct. 2014 on 309 cases of poisonous snake bites. Due to a large number of patients and severe scarcity of ASV with patches of unavailability and unaffordable high cost, low doses of ASV had to be compulsorily used for treatment of poisonous snakebites.

There is no consensus on the dose of ASV required in the management of snake bite. Low dose of snake antivenin has been found to be as effective as high dose in patients with severe neurotoxic snake envenomation. In the absence of any definite data, most recommendations are based on mouse assays. The amount of venom neutralised by 1 ml of ASV is approximately 0.6 mg for cobra and 0.45 mg for krait. Thus, empirically, the total ASV

requirement for otherwise fatal cobra and krait bites is 200 and 134 ml respectively. However, this may not be true for bites in humans, as the exact total amount of venom injected by the snake at the time of bite is variable.

Out of 216 Indian poisonous snake species there are 4 major ones; cobra, krait, Russell's viper and saw-scaled viper

METHODS

All the patients admitted for snake bite with signs of envenomation were included in this observational, prospective study. Low dose (30-50 ml) of ASV was started after testing intravenously. The patients were kept under intensive observation with supportive management in the form of artificial ventilation, neostigmine-atropine, blood and fresh frozen plasma, as needed. Vital parameters, two hourly urine output, clotting time, signs of respiratory failure, bleeding tendencies were closely monitored. All patients of neuro-paralytic snake bite also received 5 doses of 0.6 mg of injection atropine intravenously, followed by 0.5 mg neostigmine by intramuscular injection, every 30 minutes.

Statistical analysis was done with SPSS Ver. 20

RESULTS

The highest incidence of snake bite was found from July to December. Among the 309 patients, there were 161 males and 148 females (Table 1 and 2).144 patients had vasculotoxic, 122 patients neurotoxic and 43 patients mixed type of snake bites (Table 3). Of the 309 bites, only 7 snakes were brought live or killed. Majority of patients or accompanying persons had not seen or could not describe the snake.

Table 1: Age wise distribution of male patients with respect to different types of snake bite poisoning.

Age Group	Male			
Years	**Vasculotoxic**	**Neurotoxic**	**Mixed**	**Total**
12 -20	18	17	8	43
21 -30	19	26	7	52
31 -40	6	16	1	23
41 - 50	11	7	4	22
51 - 60	3	5	2	10
61-70	3	3	2	8
71-above	1	0	2	3
Grand Total	**61**	**74**	**26**	**161**

Total average dose of ASV required was 35.30 ml as shown in Table 6. (For neuroparalytic bite it was 35.41 ml, for vasculotoxic bites 32.41 ml and for mixed type 45 ml as shown in Table 3). Mortality was highest (7 out of 42 patients i.e. 16.66%) in mixed type of snake bite, followed by neurotoxic (5 patients i.e. 4.0983%) and there was no mortality among vasculotoxic snake bite patients as in Table 7.

Table 2: Age wise distribution of female patients with respect to different types of snake bite poisoning.

Age Group	Female			
Years	**Vasculotoxic**	**Neurotoxic**	**Mixed**	**Total**
12 -20	11	8	1	20
21 -30	30	12	6	48
31 -40	18	15	2	35
41 - 50	15	5	3	23
51 - 60	2	5	3	10
61-70	7	3	1	11
71- above	1	0	0	1
Grand Total	**84**	**48**	**16**	148

Table 3: Distribution of patients according to different types of snake bite with respect to average dose of ASV required.

	Type of snake bite	Total no.	Total ASV	Average ASV
Male + Female	Vasculotoxic	145	4700	32.414
	Neurotoxic	122	4320	35.41
	Mixed	42	1890	45

Table 4: Analyse 2×2 contingency table.

	Survived	Death	Total
≤40	215	6	221
>40	82	6	88
Total	297	12	309

Chi –square without Yates correction; Chi-square equals 2.839 with 1 degree of freedom. The two tailed P value equals 0.0920. The association between rows (groups) and columns (outcomes) is considered to be not quite statistically significant.

Table 5: Analyse 2×2 Contingency table.

	≤3	>3	Total
≤40	31	12	43
>40	24	13	34
Total	55	25	80

Chi –square without Yates correction; Chi-square equals 0.484 with 1 degree of freedom. The two tailed P value equals 0.4868. The association between rows (groups) and columns (outcomes) is considered to be not quite statistically significant.

There was no statistically significant difference in the survival, whether patients received more than 50 ml or low doses of ASV less than 50 ml (P= 0.0920) as shown in Table 4. 80 patients required ventilator support out of whom 11 patients required it for more than 7 days and remaining 69 patients required it for less than 7. 70%

patients required ventilator for 1 to 3 days as shown in Table 5. Among 122 patients of neuroparalytic snake bites, 62 needed artificial ventilation (50.8%). All the remaining 60 patients recovered with low dose ASV and Neostigmine and Atropine only. 15 of 42 patients of mixed bites needed ventilator, of these 8 survived. 4 of these died due to DIC and ARF, 2 already had hypoxic brain damage at admission and 1 died due to VAP (Table 8 and 11.2). 3 of 144 vasculotoxic bites needed ventilator, all survived. One elderly patient was on ventilator for mixed snake bite for 54 days was on the verge of recovery after 1 week but he developed a stroke and died after 54 days of ventilation (Table 8).

Table 6: Age wise distribution of male and female population and their average dose of ASV required.

Age group (years)	Total Male	Total Female	Total (Male + Female)
12-20	43	20	63
21-30	52	48	100
31-40	23	35	58
41-50	22	23	45
51-60	10	10	20
61-70	8	11	19
71-above	3	1	4
Total			**309**

Average ASV required 35.30744.

Table 7: No of death and survival in different types of snake bites.

	Patients survived	Average ASV required	Patients died	Average ASV required
Mixed	35	41	7	64
Neuro paralytic	117	35.47	5	34
Vasculo toxic	145	32.414	-	-
Total	297	34	12	51

Total 22 patients developed ARF (12 vasculotoxic and 10 mixed). All 12 vasculotoxic and 6 of the 10 mixed bites survived. 14 developed DIC (4 vasculotoxic, all survived and 10 mixed, 6 survived). 4 were admitted with hypoxic brain damage. (2 neuroparalytic, 2 mixed-all died) as shown in Table 10. In neuroparalytic snake bite, 3 patients died due to ventilator associated pneumonia after 5 to 8 days of mechanical ventilation and 2 patients died due to hypoxic brain damage on day 2 of ventilation (Table 11.1). In mixed snake bite, 3 patients died due to acute renal failure with disseminated intravascular coagulation after 5 to 8 days of mechanical ventilation and 1 patient died after 2 days of ventilation. Similarly 1 patient died due to ventilator associated pneumonia on day 7of ventilation and 2 patients died due to hypoxic brain damage on day 2 of ventilation (Table 11.2).

Table 8: Showing no. of days on Ventilator for Snake bite patient for recovery.

Ventilator Days	No. of patients
0	229
<1	1
1	13
2	17
3	24
4	2
5	10
6	2
7	4
8	2
9	1
10	2
25	1
54	1
Grand Total	**309**

Table 9: Table showing ASV given for neurotoxic, vasculotoxic and mixed snake bite.

ASV	Neurotoxic	Vasculotoxic	Mixed	Total
0	3	1	0	4
10	8	13	1	22
20	35	45	5	85
30	34	43	12	89
40	6	9	6	21
50	26	25	11	62
60	2	2	0	4
70	2	1	2	5
80	0	0	3	3
90	0	0	0	0
100	3	5	2	10
110	0	0	0	0
120	1	0	0	1
130	0	0	1	1
140	0	0	0	0
150	2	0	0	2
Total	122	144	43	309

Table 10: No of patients with respect to complications.

Complications	Male	Female	Total
ARF	13	9	22
DIC	6	8	14
HBD	1	1	2
RP	18	17	35
Total			73

ARF- Acute renal failure; DIC –Disseminated intravascular coagulation; HBD- Hypoxic brain damage; RP: Respiratory paralysis.

Among various reasons for preferring a particular health facility, ease of access, services free of cost, quality of services were some of the reported reasons. Most common reason for preferring to the public health facility

was that the services were free of cost. Private practitioners were preferred due to their availability and quality of care (Table 4).

Table 11.1: Causes of mortality in neuroparalytic snake bites.

Causes of mortality	Days on ventilator			Total ASV required
	0-2	3-4	5-8	
VAP	-	-	3	110
HBD	2	-	-	60
Total	5			170

Table 11.2: Causes of mortality in mixed snake bites.

Causes of mortality	Days on ventilator			Total ASV required
	0-2	3-4	5-8	
ARF with DIC	1	-	3	230
VAP	-	-	1	40
HBD	2	-	-	160

Total patients 7; Total ASV – 430.

DISCUSSION

This study started as an accidental observation as a result of non-availability or availability of very small quantities of ASV, over which we had no control whatsoever. In the vast majority of cases in this region of Marathwada in Maharashtra state of India, very low dose of ASV (about 50 ml or less) given as a single infusion over 2 hours is adequate to save cases of poisonous snake bites, provided there is a good back-up of ventilator therapy, along with intensive monitoring and supportive management.

Whole blood clotting time, girth of swelling and 2 hourly urine output are very vital bed-side observations. These small doses of ASV may not be useful in certain other regions, especially if supportive ventilatory assistance is not available. Even in such a scenario, it seems logical to give the whole dose that is planned in a single sitting as a slow infusion, instead of giving it 6 hourly. Once renal failure or local necrosis sets in, supportive management like dialysis, is more useful and life-saving rather than ASV.

In a developing country like ours, where the supply of ASV is far less than the demand, we have to use this precious life-saving drug very conservatively and judiciously.

The incidence of reactions to ASV is also minimized by careful IV testing and giving a smaller dose in a single sitting as a slow infusion. Repeating the dose 6 hourly was associated with a much higher incidence of reactions earlier. Very few snakes are brought or described by patients or accompanying persons, which does not matter, because we do not give ASV to cases who do not have any signs of envenomation even in 24 hours and the ASV available in India is polyvalent.

Between 2013- 2014, 309 patients who had signs of snake envenomation were admitted to the Medicine wards of Government Medical College, Aurangabad and were included in the study.

Symptoms of cobra bite may appear as early as 3 minute upto 6 hours. The effectiveness of cobra antivenin is inconsistent. Maintenance of adequate ventilation is essential in survivors, neurotoxic manifestations usually resolve within a week.[1] The hemorrhagins found in viperid venoms have vasculotoxic properties Adequate doses of ASV restore blood coagulability but do not reverse shock, nephrotoxicity or myotoxic signs.

Snake Venom Antiserum (Polyvalent), in India is a refined preparation of serum globulins obtained by fractionating blood from healthy hyperimmunised horses where each ml of which neutralizes the following quantities of standard venoms tested in mice by intravenous route. Cobra 0.6 mg, Common Krait 0.45 mg, Russell's Viper 0.6 mg and Saw-scaled Viper 0.45 mg.[2]

Since more than 8 years, there has been a growing scarcity of ASV due to various reasons, (including animal rights) 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. The cost of ASV is often prohibitive and if we prescribe 10 vials, the care givers may manage to buy just 1 or 2 vials and we are forced to manage the patient with whatever is available.

There is no universal consensus in many countries on the optimal dose of ASV. Higher doses have been previously used in the hope of early recovery.[3-6] 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, prior to the neurotoxins reaching their target site. Therefore, the use of large doses late in the course is unlikely to be effective.[6]

This study is an observational prospective study, which is the result of a “no choice” situation. Around 2007, we started facing a shortage of ASV. Earlier, we used to give 100 to 200 ml of ASV in patients of poisonous snake bite, though in a steady, single infusion. Many of the other physicians in this department used to prescribe 50 - 100 cc as 6 hourly doses. We believe that whatever dose is to be given should preferably be given as a single dose. The

only exceptions would be severe vasculotoxic snake bite cases when we may repeat a dose. Even in these cases, the mainstay of treatment is fresh frozen plasma and blood, monitored by the 20 minutes whole blood clotting time.

Antivenins are useless in isolated soft tissue swelling that may even be caused by non-poisonous snakes. In poisonous bites also, the effect of antivenins in preventing tissue damage by necrotising venoms is limited as venom components bind to local tissues quickly. Once neurotoxicity is established and endotracheal intubation is required, further doses of antivenin are unlikely to be beneficial.[7]

ASV is useful when the toxin is circulating in the blood and not useful when it gets attached to the kidneys or nervous system. It is of no benefit in reversing effects that have already been established, e.g. renal failure, established paralysis, necrosis.[5,8] Hence there is not much rationale in giving it 6 hourly as many regimes say.[8] In earlier days, we used to get many allergic and few anaphylactic reactions to ASV. With the small doses that we have been using recently, we saw only 4 cases of allergic reaction and could give ASV in 3 of these.

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. The body's detoxifying system will bring down the clotting time eventually though it may take a slightly longer time. Administration of a bottle of fresh blood is often helpful in bringing down the clotting time further, without any additional dose of ASV.[9] Locally developed snakebite management protocol significantly reduced overall anti snake venom utilization in West Bengal, India and such protocols should be encouraged.[10]

After the scarcity of ASV set in, we observed with surprise that there were patients in whom ASV could be given in very small quantities (10 to 50 cc only) who recovered. Indeed, there were three cases for whom no ASV was available, who recovered with supportive management.

When the scarcity continued, we observed that the vast majority of patients of neuroparalytic snake bites recovered with less than 50 cc of ASV given as a single infusion provided there was a strong backup of ventilator assistance. Many studies now report that the benefit of large doses of ASV is questionable.[11] We also observed that neostigmine – atropine combination helped in the improvement and has been using this regularly.

Slight male preponderance is seen in our study (161 males and 148 females) that may be attributed to their outdoor activities and occupational exposure as farmers or herdsmen. Young male agricultural workers were the most commonly affected group in our study (30.94 % patients in the age group 12 to 30 years). This is similar to other studies.[9-11]

Most of the cases occurred during the month of June to December, which is the monsoon season.[9] Maximum events of envenomation were seen with vasculotoxic snakebites (144) followed by neurotoxic (122), followed by mixed type (43), The mortality was highest in mixed type of snake bite (7) followed by neuro toxic (5) and there was no mortality in the vasculotoxic group. Hemotoxic bites were the commonest snake bites attributable to vipers,[3] followed by neurotoxic cobra bites. Simultaneous neurotoxic and hemotoxic manifestations in patients were attributable to kraits.[12, 13]

All the 5 patients of 122 neuroparalytic patients who died came late to our hospital, 2 of them already had hypoxic brain damage and 2 had to be given cardiopulmonary resuscitation in the casualty. They were on the ventilator for 1-8 days. 7 out of 42 patients of mixed envenomation who died had developed hypoxic brain damage as well as acute renal failure with disseminated intravascular coagulation. They also needed ventilation for 1-8 days.

As observed with viper, in cobra envenomation also, there is no significant alteration in the effect or outcome whether we give low dose or higher dose of ASV. Of the 43 patients, identified to have bitten by Krait, 7 expired. Since Krait bites are usually painless with mild local symptoms, victims might not have recognized the bite resulting in delayed hospitalization.

5 of the 122 neurotoxic snake bite cases who died had presented late to the hospital and already had undergone cardiopulmonary resuscitation and had hypoxic brain damage .In the mixed type, 7 patients died due to acute renal failure with disseminated intravascular coagulation, septicaemia and hypoxic brain damage. However, practically all the patients who survived did so with very low doses of ASV (35 ml). Also according to the study carried out by Dr. Punde et al patients of mortality group received more ASV than those of survival group.[14]

CONCLUSION

The observation that very low dose of ASV (less than 50 ml) is adequate to save lives of victims of poisonous snake bites provided they get good supportive management and come early to hospital is very important in developing countries like India, where there is high incidence of poisonous snake bites and scarcity of ASV.[15]

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