DOI: 10.14260/jemds/2014/3084

ORIGINAL ARTICLE

A TRIAL OF LOW DOSE ANTI SNAKE VENOM IN THE TREATMENT OF POISONOUS SNAKE BITES IN BRIMS TEACHING HOSPITAL, BIDAR

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HOW TO CITE THIS ARTICLE:
Vijay Kumar B. A, Sachin Gudge, Shivkumar Mithare, Satish Mudbi, Shahank Kulkarni. "A Trial of Low Dose Anti Snake Venom in the Treatment of Poisonous Snake bites in Brims Teaching Hospital, Bidar". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 30, July 28; Page: 8544-8551,
DOI: 10.14260/jemds/2014/3084

ABSTRACT: OBJECTIVE: To demonstrate that use of lower doses of anti-snake venom is as effective as high doses and it is associated with less complications and lower mortality especially in the wake of rising cost of medical treatment, the people most affected by snake bites being the poor farmers. **METHODOLOGY**: A Prospective descriptive studies consisting of 50 Snake bite patients fulfilling the inclusion criteria that were admitted to BRIMS, Bidar from 2011 to 2013 and were treated with a low dose ASV regime. The patients were initial given 2 vials of ASV followed later with I vial at a time according to clotting time. Any other supportive measures were undertaken as necessary. **RESULTS:** In this study the average dose of ASV required was only 6.70±3.24 vitals. The complications – 12.9% patients had ARF, and another 12.9% patients had neuro-paralysis sever enough to require ventilatory support. There were 2 deaths (mortality of 3.7%) in the study. **CONCLUSION:** Low dose ASV regime in poisonous snake bites along with supportive treatment as necessary is as good as high dose regime and has lesser adverse effects while reducing the cost of treatment too. Hence low dose regime can be used with beneficial results in poisonous snake bites.
KEYWORDS: ASV, Neurological Manifestation, Shock.

INTRODUCTION: Snake bite is a major problem in rural India with more than 2lakh snake bites being reported in India annually of which 35, 000-50, 000 die.[1, 2] A national 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 snake bite deaths nationally (99% CI 40, 900 to 50, 900).[3]

The only specific antidote for snakebite is administration of Anti snake venom (ASV) with or without adjunctive treatment as necessary in each case. Albert Calmeete introduced serum antivenom use for the treatment of envenoming in 1895 against the Indian cobra (Naja naja)[4] in India and by Lepinay in Vietnam. The latter reported the first successful use of anti -venom serum therapy in patients in 1896.[5] It has been in use since then with few formal clinical trials as to the right dose of anti-venom required for treatment.

The hitch with determining the optimum ASV dose is the quantity of venom injected at a bite is a variable depending on the species and size of the snake, the mechanical efficiency 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.

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 anti-venom must occur almost immediately after venom enters the circulation to significantly impact on recovery time of the coagulopathy due top envenomation.[7]

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ASV used in India polyvalent and contains anti-venom against cobra, Russell's viper, krait, saw scaled viper. Each vial of ASV containing 10ml of anti-venom cost about Rs. 500. 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 refined animal serum product some patient develops hypersensitivity reactions to it. In our experience, if a patient is allergic to ASV he can be given ASV after I.V. antihistamines (Pheneramine) and Hydrocortisone or in severe cases Adrenaline.[4, 9] Recent Sri Lankan data comparing premedication of 1007 snake bite victims with prothazine, hydrocortisone and low dose adrenaline, alone and various combinations showed statistically significant reduction in the overall high rate of early adverse reaction (77%) in the promethazine alone group where a 33% reduction in pruritus, urticaria, facial oedema and bronchospasm was observed.[8] Alternatively, the patient may also be desensitized by giving gradually increasing doses of ASV. If still intolerant the patient may have to be treated only with adjunctive or supportive treatment.[9]

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 good as or even better (less complications) than high dose ASV.[10-13] Despite evidence from smaller doses from evidence – based medicine, most centres are still using large doses. We in our centre have been using low dose ASV as a routine since many years and wish the same could be implemented in other hospitals also with enough evidence for it. The many uncertainties in this area and research work regarding this being scanty instigated the pursuance of the present study.

MATERIAL AND METHODS: A prospective descriptive cohort study consisting of 50 snake bite patients was undertaken to study the efficacy of low dose anti snake venom in the treatment of patient with poisonous snake bites. A total of 100 snake bite patient presented to out hospital between 2011 to 2013, of which 54 patient who were aged ≥15 years with history of snake bite within the previous 24hrs 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), neurotoxic signs such as ptosis, external ophthalmoplegia, falling single breath count, respiratory muscle paralysis – falling S_PO_2, hypotension (B.P.<90/60 mm of Hg)s, shock (requiring ion tropic support), cardiac arrhythmia, abnormal ECG, Acute Renal Failure evidenced by oliguria, anuria, rising creatinine (>1.5mg/dl) albuminuria, hemoglobinuria/ myoglobinuria, dark brown urine were found eligible for the study.

The other 32 patients were excluded as 19 of them did not have any signs if envenomation. 11 of them had already been treated elsewhere previously, 1 patient presented after 24 hours of the bite and one was brought to casualty gasping and could not be resuscitated.

All patient fulfilling the inclusion criteria were admitted t the ICU and were given ASV in 100ml 0.9 normal saline as follows: 2 vials of ASV in 100ml NS over 1hr and then clotting time repeated half an hour after completion of the ASV, if CT was prolonged I vial of ASV in 100ml NS was given over 4 hrs and CT repeated but if CT was normal 1 vial of ASV in 500ML NS was given over 24 hrs and then CT repeated after completion. If repeat CT was again prolonged 1 vial of ASV was given CT repeated and the same continued till CT was normal after a 24hrs dose of ASV. All patients were

given Tetanus toxoid and were pre-medicated with inj. Pheneramine and Inj. Hydrocortisone 100mg intravenously. Any other supportive measures as necessary such as antibiotics and surgical intervention for Cellulitis – fasciotomy, ventilatory support and Noestigmine for neuro-paralysis with respiratory distress, Fresh frozen plasma/ blood, dialysis, inotropic support was given.

Statistical Analysis: For the purpose of analysis patient were grouped based on the degree of derangement of the clotting time, presence of renal failure or albuminuria, severity of neuromuscular paralysis, presence of hypotension into mild (clotting time of 10-14 minutes, no renal failure or albuminuria, mild neuro-paralysis without respiratory muscle involvement and not requiring ventilatory support normal blood pressure), moderate (clotting time of 15-30 minutes, mild renal failure – creatinine <2mg/dl or 1+ albuminuria, mild respiratory paralysis not requiring ventilatory support, normal blood pressure) and severe (clotting time of >30 minutes, severe renal failure – creatinine >2mg/dl or 2+ or more albuminuria, requiring ventilatory support, hypotension.

Results on continuous measurements are presented as Mean ±SD (min-Max) and results on categorical measurements are presented in number (%) significance is assessed at 5% level of significance. Analysis of variance (ANOVA) has been used to find the significance of study parameters between the three groups of patients. Chi-square test has been used to find the significance of difference of study parameters on categorical scale between the groups. 95% confidence Interval has been computed to find the significant features.

OBSERVATIONS AND RESULTS: The baseline characteristics of the study population was as follows Average age of the patients was 35.72±14.42. Most of them were in the 20-40 years age group (52%) and 70% of the victims were males, also 68.5% that is almost two thirds of them were farmers. There were 2 peak seasons – once in the summer of May and June and again in the month of October and November. 70% of the patients presented within 4 hours of the bite 87.1% of them within 6 hours – a significant improvement compared to previous studies probably owing to better transport facilities and awareness among people regarding snake bites.

50 patients (98%) had haemostatic abnormalities (deranged clotting time). One patient out of the total of 10 patients (18.5%) had signs or neuromuscular paralysis alone with a normal clotting time as against the other patients who had both neurological and hematologic involvement. There was no cardiac involvement in any of the patients. Serum Creatine kinase level was done in 5 of the patients suspecting rhabdomyolysis and was found to be raised in all of them.

69.9% of the bites were on the lower limbs. All patients had local inflammation at the site of the bite. The local reaction secondary to the bite was usually mild (74% of the patients). However 2 patients (3.5%) had severe local reaction and later developed cellulitis going on to abscess formation in one case requiring incision and drainage and the other patient had necrotizing fascitis which was managed with appropriate antibiotics and later a split thickness skin grafting was done.

58.9% patients had mild derangement of hemostasis with a clotting time of 10-14 minutes, 11.9% had moderate derangement with a clotting time 15-30 minutes and 26.8% had sever derangement of hemostasis with a clotting time of <30minutes or incoagulable blood.

As already discussed the patients were grouped into 3 categories for analysis. Based on these parameters of the 50 patients, 23 patients (42.59%) had mild envenomation, 8 (14.81%) had moderate envenomation and 23 (42.59%) had severe envenomation. Complications of snake bite

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were higher among patients with severe envenomation especially cellulitis, DIC, Septic shock, Acute renal failure though only one patient in the severely envenomated group required dialysis. The need for supportive measures was seen only in the severe envenomation group probably since they were grouped on the basis of overall patient characteristics and not just the severity of coagulation derangement which may vary in severity depending on the snake species and constituents of the venom. The basis of grouping of these patients and other patient characteristics is as show in the table.

Most patients that are 68.5% could be managed with 4-7vials of ASV 24.1% required 8.11 vials and only 7.4% patients needed 12 or more vials of ASV. The average dose of ASV required was 6.70±3.24 vials ranging from 5.22±1.86 vials in mild cases to 8.78±3.68 vials in severe cases the maximum dose used was 19 vials in one patient in whom the clotting time never corrected on treatment even after transfusing fresh frozen plasma.

Hence ASV was stopped as the patient had clinically improved with no other signs of envenomation or any bleeding manifestations. The patient was called for review 15 days following discharge and clotting time was rechecked, it had normalized. Only 3 (5.6%) of the total of 50 patients had allergic reaction to ASV (table 2).

We also noted that the requirement of ASV was independent of the bite to needle time as opposed to the severity of envenomation even patients presenting after 6 hours of the bite could be managed with 7.142857±4.450789 but severely envenomated patients among them require 13±4.242641.

There were 2 (3.7% deaths (table 3), both with severe envenomation, had presented more than 6hours after snake bite and one of them developed DIC and the other patient was in shock at presentation and went on to develop multiorgan dysfunction.

Variable	Severity of envenomation			All cases (n=50)	P Value
	Mild (n=23)	Moderate (n=8)	Severe (n=23)		
SBP	127±16.1	132.00±14.06	123.13±18.14	126.07±16.71	0.6978
DBP	80.9±11.2	83.75±7.44	79.82±12.09	80.85±11.06	0.3654
Neuro-paralysis	2 (18.18%)	2 (18.18%)	7 (63.6%)	11 (20.4%)	0.1760
Total count	10443±3504.9	9812.5±3745.26	14700±6753.72	12162.96±5549.37	0.0119
Platelet count	267087±86892.78	280625±81566.69	235304±80542.2	251037.7±98066.5	0.2932
Creatinine	1.017±0.16	0.9±0.25	1.19±0.47	1.19±0.66	0.0751
Albuminuria	0	2 (15.4%)	11 (84.6%)	13(24.07%)	0.007

Table 1: Patient characteristics according to severity of envenomation

**P<0.05; (SBP – Systolic Blood Pressure, DBP- Diast0lic Blood Pressure)

	Mild (n=23)	Moderate (n=8)	Severe (n=23)	P Value
Bite to needle				
0-2 hours (20)	9	4	7	0.4808
2-4 hours (18)	9	1	8	0.0669
4-6 hours (9)	3	1	5	0.3575
>hours (7)	2	2	3	0.9015
Cellulitis	6 (23.1%)	2 (7.7%)	18 (69.2%)	0.0007

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Respiratory	0	0	7 (30.45%)	0.0044
Paralysis Renal failure	0	2 (5%)	12(52.2%)	0.0003
Need for dialysis	0	0	1 (4.2%)	0.5033
Shock	0	0	2 (8.4%)	0.2467
DIC	0	0	1(4.2%)	0.5033
Transfusion (FFP/ Blood)	0	0	15(65.2%)	<0.0001**
Fasciotomy	0	0	7(30.4%)	0.0044
Ionotropes	0	0	2(8.7%)	0.2467
Ventilatory	0	0	7(30.4%)	0.0044
Support Average no. of Vials ASV	5.22±1.86	5±1.7	8.78±3.68	<0.0001
Reaction to ASV	2(8.4%)	0	1(4.2%)	0.6167
Days of ICU Ward Stay	3.96±1.02	3.88±1.25	7.17±3.18	<0.0001
Mortality	0	0	2(8.7%)	0.2467

Table 2: Table showing complications, treatment details outcome patients

**P<0.05; (DIC- Disseminated intravascular coagulation; FFP- Fresh Frozen Plasma; ICU- Intensive Care Unit)

Variable	**Bite to needle time**					**P value**
	0-2hrs	**2-4hrs**	**4-6hrs**	**>6hrs**	**All patients**	
Recovered	20 (38.5%)	16.34.6%)	8(17.3%)	4(9.6%)	48 (100.0%)	0.015*
Died	0	0	0	2(100.0%)	2(100.0%)	0.015*
Total	**20(37.1%)**	**16(33.3%)**	**8(16.7%)**	**6(12.9%)**	**50(100.0%)**	

Table 3: Outcome according to bite to needle time

DISCUSSION: There is evidence for smaller doses from past studies but many centers are still using large doses. Guidelines also suggest high doses of ASV probably because of the small number of studies hence obviating the need for more studies to prove the same.

In this study the average dose of ASV required has only been 6.70±3.24 vials and the maximum that was used was 19 vials only one patient. The complications (12.9% patients has ARF and another 12.9% patients had neuro-paralysis severe enough to required ventilatory support) and hard outcomes (mortality of 3.7%) have been much better than studies using high doses (26%) had ARF and there was 14% mortality in the high dose group in the study by Paul et al; 60% had ARF and there was 30% mortality in the high dose group in the study by Sriman narayana et al, table 4 and 5).

Also the quantity of anti- venom used was independent of the bite to needle time and is more closely related to the severity of envenomation probably because the neutralizing dose depends on the type and quantity of venom injected.

The adverse reaction to ASV has also been low (5.6%) as against 26.6% in the high dose group in the study by Sriman narayana et al. also since the dose ASV is much smaller than conventional regimes which sue 10-25 vials of ASV it is much more economical while being equally efficacious and has lesser adverse reactions and is more economical when compared to higher doses.

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Investigation	Avg dose of ASV (Vials)	ARF or Dialysis (% of patients)	Ventilation (% of patients)	Adverse reaction to ASV (% of patients)	Mortality (% of patients)
Tariang et al	4.7±2.7	0%	3.4%	NA	0%
Srimannarayana et al	20.5±4.3	50%	Na	16.67%	20%
Paul et al	6	18%	6%	NA	10%
This study	6.70±3.24	12.9%	12.9%	5.6%	3.7%

Table 4: Low dose ASV studies

(ARF- Acute Renal Failure)

Investigation	Avg dose of ASV (Vials)	ARF or dialysis (% of patients)	Ventilation (%of patients)	Adverse reaction to ASV (% of patients)	Mortality (% of Patients)
Tariang et al	8.9±3.5	0%	6.4%	NA	0%
Srimannarayana et al	37.6±20.5	56.7%	NA	26.67%	30%
Paul et al	12	26%	6%	NA	14%

Table 5: High Dose ASV studies

CONCLUSION: This study has thus demonstrated that low dose ASV regime in poisonous snake bites irrespective of the severity along with supportive treatment as necessary is as efficacious as high dose regime, and has lesser adverse effects. It also lowers the cost of treatment as each vial of ASV cost about Rs.500. and a reduction in requirement of 5-10 vials of ASV reduces the drug cost alone by Rs.2500 to 5000. Hence, low dose regime can be used with beneficial results in poisonous snakebites.

In fact Isbister et al in their study demonstrated that neither earlier administration of anti-venom nor higher doses of anti-venom reduced time to recovery venom-induced consumption coagulopathy. However, early administration of FFP was associated with faster recovery. The effect of anti-venom was best when administered within 1 hours.[7] In a previous study by the same author where thrombotic microangiopathy resulting from brown snake bite was treated with ASV, dialysis, plasmapheresis it was noted that prognosis was good and management should focus on early anti-venom therapy and supportive care.[14]

Also newer areas of development should be looked at such as the use of isolated toxic fractions that could increase the protective titer of the anti-venom and reduce the quantity of anti-venom administered, while avoiding the formation of antibodies against non-toxic proteins,[15] Affinity purifications of anti-venom enables the preservation of specific antibody only.[15]

The cloning of toxins of hydrophidae or Crotalida[16],[17] may be a first step in the production of new anti-venom for therapy. The use of more immunogenic recombinant variants,[18] preparation, of toxoids using various physicochemical processes[19] or molecular techniques are also being tries. Recently venom has been incorporated into stabilized sphingomyelin- cholesterol liposomes. The administration of such preparations, through injection or oral route is followed by a rapid increase of specific protective antibodies.[20]

Until we are able to find a solution to this huge problem of shortage of ASV we should try to use it judiciously and as necessary.

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Date of Submission: 26/06/2014.
Date of Peer Review: 27/06/2014.
Date of Acceptance: 15/07/2014.
Date of Publishing: 28/07/2014.