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A Prospective Study of Coagulation Profile and Outcome of Management of Compartment Syndrome in Snake Bite

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Abstract

BACKGROUND: Most of the venomous snake bites results in hemorrhage and coagulopathy. Local effects require regular monitoring for early recognition of compartment syndrome. Incidence of complications is directly proportional to the duration of venom in blood prior to neutralization by Anti snake venom due to late arrival of the patient at Hospital [1]. Coagulopathy is a common manifestation in cases of snake bite and can be detected by blood coagulation tests, an early identification of which can reduce mortality and hospital stay.[2] Primary objective is to predict morbidity and mortality in snake bite cases with the timing of administration of Anti snake venom, Secondary objective is to study the outcome of management of acute compartment syndrome and coagulation profile in snake bite.

MATERIALS AND METHODS: The study was carried out during the period November 2016 to September 2018 in a tertiary hospital Bangalore and 48 patients were included in the study. The detailed history, clinical examination and all the relevant laboratory investigations were done. We have studied the coagulation profile, compartment pressure and the relation of Anti snake venom (ASV) administration time with morbidity and mortality.

RESULTS: Early and cautious use of ASV reduced hospital stay and made statistically significant difference in terms of outcome in our patients (P value 0.005)

CONCLUSION: Early and cautious use of ASV influences the outcome in snake bite cases and measurement of compartment syndrome is strongly recommended as it helped in our cases to avoid unnecessary painful procedure and long hospital stay.

Keywords: ASV, COMPARTMENT SYNDROME, SANKE BITE

INTRODUCTION

Snake bite is a major health problem in India and other tropical countries. In India there are around 216 species of snakes spread in different habitats. The four most common venomous snakes found in India are Naja naja (Cobra), Bungarus caeruleus (Krait), Echis carinatus (Saw scaled viper) and Daboia russelii (Russel's viper)1. Among the Viperidae class there are true vipers and pit vipers accounting to 26 species. Russell's viper is associated with high mortality which is true viper, other important vipers are saw scaled vipers which are considered to be one of the deadliest snakes. Elapids are other major family with many terrestrial species, mainly including Cobras, King Cobras, Kraits and Coral snakes. While clinical

presentation of snake bite varies as per the snake species, most of the snake bites are non-venomous, said that 50% of bites are Dry bite.

The common clinical features following local toxicity are pain, skin necrosis burning sensation and edema. Systemic toxicity depends on species that bites whether hemotoxic or neurotoxic or myotoxic or both. Neurotoxic bites present as drowsiness, paresthesia, ptosis, paralysis of facial muscles, external ophthalmoplegia, respiratory paralysis and generalized flaccid paralysis. While hemotoxic bites present as bleeding from bite sites, other wounds or gums or hematuria due to coagulopathy. When the snake is not recognized and antivenom is nonspecific a syndromic approach recommended by WHO guideline 2016 is helpful. Syndrome 1: Local envenoming signs with bleeding/clotting Disturbances- (Viperidae), Syndrome 2: Local envenoming with bleeding/clotting disturbances, shock or acute kidney injury- (Russell's viper); With bilateral ptosis, external ophthalmoplegia, facial paralysis etc. and dark brown urine- (Russell's viper), Syndrome 3: Local envenoming with paralysis- cobra or king cobra, Syndrome 4: Paralysis with minimal or no local envenoming bitten on land while sleeping on the ground with/without abdominal pain- (Krait), Syndrome 5: Paralysis with dark brown urine and acute kidney injury: Bitten on land (with /clotting disturbance) – (Russell's / Hump nose viper)

Another clinical feature suggestive of cobra bite differentiating it from Krait is the local signs of pain, necrosis, and swelling at the site of bite which is seen in cobra and never in krait bites.

Neostigmine is another way of differentiating, and cobra venom is postsynaptic that can be reversed using neostigmine with atropine. The reversal is seen within minutes, and it can be repeated. If the patient shows signs of bleeding or nephrotoxicity in addition; then, we should consider Russell's viper bite. Russell's venom is unresponsive to neostigmine, and it should not be repeated if there is no improvement in ptosis after the first dose within one hour. Some snake venom like Russell's vipers cause consumption coagulopathy within few minutes of bite as contains several anti-hemostatic factors and result in hemorrhage. Most common presentation of these patients is oliguria or anuria. It is seen subsequent to Russell's viper in majority of the cases, also by Saw Scaled Viper, Krait and Cobra either direct toxicity by snake venom or secondary to multiple complications set in by toxicity like hypotension, intravascular hemolysis and DIC, rhabdomyolysis2.

Anti-snake venom (ASV) is the treatment of choice for venomous bite. Early ASV is the main stay as it prevents from developing complications. Children and Pregnant should receive the same ASV dosage as others because the ASV is targeted to neutralize the venom and venom injected by snake bite does not vary. The ASV that is used is polyvalent and covers 4 big poisonous snakes The Indian Cobra, The common krait, The Russell's Viper and The Saw Scaled Viper. Emergence of fatal snakes like humped nose viper, Malabar pit viper has made the polyvalent obsolete in cases bitten by them. In case of severe anaphylaxis injection hydrocortisone 100mg IV and Chlorpheniramine 2 mg IV should be given and ASV should be given after desensitization. Neostigmine is an anticholinesterase, which is particularly effective in postsynaptic neurotoxins such as those of cobra and is not useful against presynaptic neurotoxin i.e. common Krait and the Russell's viper.

Post snake bite compartment syndrome is another worrisome complication as it causes significant morbidity and increases length of stay in hospital. Compartment syndrome is increase in tissue pressure which exceeds the perfusion pressure in a closed facial space leading to nerve and muscle ischemia and resulting in muscle necrosis if not intervened on time. Normal pressure of tissue falls between 0 to 8 mmHg, clinical findings associated with acute compartment syndrome generally correlate to a degree to which tissue perfusion pressure within the affected compartment approaches the systemic blood pressure. Capillary blood flow becomes compromised when tissue pressure increases to 25- 30 mmHg of Mean arterial pressure. Pain develops when pressure reaches between 20 – 30 mmHg. Ischemia occurs when tissue pressure approaches the diastolic pressure. Higher compartment pressure may be necessary before injury occurs to peripheral nerves in patient with systemic hypertension, while acute compartment syndrome may develop at lower pressure in those with hypotension or peripheral vascular disease. Tissue damage in compartment syndrome may be reversible if intervened within 3 -4 hours, by 6 hours variable damage will be done and by 8 hours irreversible changes set in. Prophylactic fasciotomy is done in

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many set ups when cellulitis with edema and pain is noticed but studies show fasciotomy does more harm than good so it should be delayed unless compartment syndrome is present.

OBJECTIVES

The primary objective is to predict morbidity and mortality in snake bite cases with the timing of administration of ASV. Secondary objectives are outcome of management of acute compartment syndrome and study of coagulation profile in snakebite.

METHODOLOGY

A prospective study entitled "A PROSPECTIVE STUDY OF COAGULATION PROFILE AND OUTCOME OF MANAGEMENT OF COMPARTMENT SYNDROME IN SNAKE BITE" was undertaken at a tertiary hospital in Bangalore after the approval from Ethics Committee.

The study was carried out in the period of November 2016 to September 2018. All patients above 18 years who presented with complaints of snake bite to the Emergency Department (ED) were included in the study except patients with preexisting deranged International normalized ratio (INR >1.5). The detailed history, clinical examination and all the relevant laboratory investigations were done including whole blood clotting time (WBCT). In the present study, the standards and criteria were adapted from the WHO guidelines for snake bite and quick reference guidelines by government of India.

All the patients WBCT were checked before Anti snake venom (ASV) was started and there after WBCT was measured 6th hourly or as required. To do WBCT take a glass test tube or bottle preferably new and put 2ml of venous blood drawn in it and look after 20 minutes and not before that by tilting the tube. The tube should be left in place at room temperature. When the blood is clotted test should be carried out every one hour from admission for 3 hours and when the blood is not clotted then every 6th hourly the test is to be done after administration of loading dose of ASV. If it is a neurotoxic envenomation then every 6th hourly WBCT has been recommended. Though WBCT is said to be a simple bed side test it has may false values. WBCT >20 minutes with clinical signs ASV is given.

Compartment pressure was measured when clinical features of compartment syndrome were seen. The early symptom to develop is excruciating out of proportion pain, aggravated pain on passive stretching, Pain, Pallor, Paresthesia, Pulselesness, Paralysis Poikilothermic. Compartment pressure are to be regularly monitored when compartment syndrome is suspected and is measured by inserting a 16G needle in the suspected compartment at a depth of 1 cm and connects to simple tubing irrigated with normal saline. Measure rises in the saline column in the tubing. A rise more than 40 cm of saline corresponds to 30mm Hg of Lymphatic/ capillary pressure and is suggestive of compartment pressure. Fasciotomy is done when compartment pressure is more than 30 mmHg

INR was taken into consideration for transfusion of blood products in case of coagulopathy. We are analyzing the outcome of venomous snake bite with the ASV administration time. Identification of snake was confirmed by snake pictures shown to the patient or in some cases where snake was brought to ED by the attenders.

Method of Statistical Analysis:

The following methods of statistical analysis have been used in this study. The results for each parameter (numbers and percentages) for discrete data and averaged (mean + standard deviation) for continuous data are presented in Table and Figure. Proportions were compared using Chi-square test of significance. Cochran's Q Test will tell you if there is a difference between the two variables. If you reject the null hypothesis (i.e. the test identifies differences, Cochran's Q test is used to identify the areas which have differences. Kruskal wallis test. This was used to compare two or more independent samples. It extends the Mann-Whitney test and indicates stochastic dominance of one group over other.

RESULTS

The study was carried out in the period of November 2016 to September 2018 and 48 patients were included in the study. Incidence of snake bites was seen more in Males (75%) than females (25%) Age wise distribution of cases shows 21-40 years old group were bitten more than other age groups. Cases from Rural population (68.80 %) was more in number than urban 31.30 %. These observation shows that snake bite is an occupational health hazard involving people of

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working age group from agricultural area. 64.60 % cases were referred cases from peripheral institutes either because of poor health facilities or lack of trained doctors and lack of knowledge of patients which delayed the time in administration of ASV.

Seasonal trends in snake bite with maximum number of cases were seen in rainy season 37.35% but the maximum number of cases were seen in month of November 16.7%. Among the types of bite, 7 cases (14.5%) were dry bite (bite by a venomous snake in which no venom is released), 2 (4.2%) were neurotoxic (bite by a venomous snake resulting neuroparalytic manifestations) and rest 39 (81.3%) were hemotoxic (a venomous snake bite resulting in bleeding manifestations). In patients who were given ASV, WBCT before and after ASV administration was compared and P-Value was significant Table 1.

The clinical features reported among the study subjects, 75 % (36 Patients of 48) had local signs of envenomation on presentation 4.16 % (2 Patients) had pure neurological presentation 12.5% (6 Patients) had neurological signs plus local signs of toxicity 20.8 % (10 Patients) had neither Neurological nor local signs of envenomation. Compartment pressure measurement among the cases of which 13 Patients (27.1 %) were suspected to have compartment syndrome based on clinical grounds and compartment pressure was measured in them, of which 11 were having high compartment pressure (> 30 mmHg). Of 13 patients in whom compartment pressure was recorded, 11 underwent fasciotomy and 2 were managed conservatively who were discharged early and dint have to undergo the painful procedure and long healing process Table 2. One Patient had permanent disability who underwent amputation of both lower limbs, who had not received ASV till 96 hours post bite.

Table 3 shows 37.5 % Patients had high INR (>1.5) on day of bite which came to normal with ASV administration and blood products and the study is statistically significant. In us on day 1 of bite 37.5% (18 Patients) had altered INR for which ASV and blood products were given, on day 2 only 8.3 % (4 patients) continued to have relatively high INR for which ASV was continued, Day 3 only 2.1 % (1 patient) of those 18 had high INR. On Day 4 all patients who were having high INR were normalized after ASV was completed hence it was statistically significant. Platelet and Hemoglobin trend was seen in all patients to assess risk of coagulopathy, in spite of ASV administration there was a fall in hemoglobin over first 3 days and fall in platelet over two days, the P-Value was >0.05 hence it was not statistically significant.

Renal function test (RFT) and liver function test (LFT) derangements among cases studied, 31.7 % (13 Patients) had acute kidney injury (AKI) and 14.6 % (6 Patients) underwent hemodialysis. Liver enzymes were measured on day one and after 48 hours, rising trend was noticed even with ASV administration, P-Value derived was >0.05 and it was not statistically significant.

Table 4 shows administration of ASV as early if given within 6 hours and late if given after 6 hours of bite. Of the 41 Patients given ASV 32(66.7%) were administered early and 9(18.8%) were administered late While 31(64.6%) patients were given 30 vials and 10 (20.8%) of them were given less than 30 vials of ASV. Our study showed a statistically significant difference in terms of recovery days when we compared the patients who were given ASV early, late and the dry bite cases that were not given ASV. The means for early ASV is 11.8, late is 13.3 and for dry bites is 1.9. In our study we have seen 4.9 % (2 Patients) of cases among those who were administered ASV had urticarial rashes to ASV.

Comparing the proportion of complications of early and late ASV administration groups, outcome of dry bites who were not given ASV and early ASV groups was better than people administered late ASV shown in (Table 5). Proportion of complicated cases was more in late ASV group and the study was statistically significant.

DISCUSSION

Snake bite contributes to significant load of cases presenting to emergency department. Knowledge in depth about snake bite envenomation and its features is necessary to reduce the morbidity and financial burden to subjects to avoid unnecessary ASV administration and procedures. Distribution of cases were studied as rural and non-rural in our study we saw 68.80% were from rural background and rest from the extension areas of cities /semi urban areas. Other studies like Sharma et al, Bhalla et al, El Hattimy et al shows similarly high proportion of rural cases3,4,5.

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This could be because of the habitat of the snakes which is the agricultural area and forest areas targeting the farmers or the semi urban areas where construction is being done targeting the laborers, that is how it is an occupational health hazard.

In our study summer as March to May, winter between October to February and monsoon June to September. Our cases were seen are as maximum number of cases were seen in rainy season 37.35% followed by summer 29.05% but the maximum number of cases were seen in month of November 16.7%., Bhalla et al showed maximum cases during summer 51.33%3, Pandey et al showed maximum cases spread during monsoon, In June and August (26% in each month) followed by September (21%) making total of 73%6 and S Paulo et al also described seasonal pattern of snakebite, with an increase in the rainy season7. Roriz et al studied 78.3 percent of case during November to april which is amazons rainy reason8. This seasonal trend has been explained as due to an increased activity of both snakes and humans during this period, cropping season or increase in number of preys. It is at the start of working hours in the early morning or night hours when most the bites are reported because of inadequate sunlight.

Comparison with other studies of Punde et al, Singh et al, Deghani et al and Bhalla et al our study showed more incidence of venomous snake bites and low incidence of non-venomous snake bites this could probably be because our Institute is located in Urban area and we received maximum of the referred cases from the peripheries and the stable cases would have been managed conservatively and not referred9,10,11. In our study of snake envenomation characteristic revealed that maximum number of snakes was hemotoxic / vasculotoxic (95.1%) and very less percentage were neurotoxic (4.9%). Other studies by Bawaskar et al, Hyat et al, Meenakshi et al also reveal the same characteristic of poisoning with vasculotoxic / hemotoxic envenomation being dominant12,13,14. Down south in India neurotoxic snakes are less and viper bites are more due to geographical distribution.

In our study population 18.8 % had approached first for herbal medicine while studies done in other hospital 18.8% of the victims initially consulted a traditional healer in our study, in study by Rupal Padhiyar et al it showed 22% 15 and a study in Kenyan population by snow r et al showed (68%) of bite cases sought herbal treatment16. It is basically the awareness of the people in a locality and resource availability that makes these figures vary from place to place. WBCT before and after ASV was done in 41 cases in our study to look for coagulopathy due to envenomation and it was studied that 25 (61%) cases of those had WBCT >20 minutes and after ASV WBCT was >20 minutes only in 4 cases (9.8%). The WBCT20 was not intended as a clotting test per se but as an indicator of envenoming (and need for antivenom) in patients bitten by snakes that cause coagulopathy17. In patients who were administered ASV, WBCT was done before and after it was found that it was >20 minutes before ASV and <20 minutes in maximum number of patients after ASV. In our patients WBCT was not considered sole criteria to start ASV and clinical signs were given weightage.

As mentioned in Ibister et al there has been delay in administration of ASV when there was negative WBCT. Specificity and sensitivity of WBCT becomes questionable also because of improper methods of doing the test. There have not been any standard recognized methods of doing WBCT except the guidelines of WHO and GOI which mention the method of going it, so many things alter the results or falsify the results as human errors bound to happen in our Indian set up with inadequate staff and patient ratio. Reaction to ASV was noticed in only 4.9% of our cases while few studies like Deshpande et al have shown high incidence of reaction to ASV (56.10%) while in a study by Amin et al showed ASV reaction from mild to severe in 88.5% 18,19. The study by Poovazhagi et al on ASV reaction in children showed maximum incidence of ASV reaction in children20. Our study did not take fever, chills, headache as reactions to ASV as these could not be proved specific to ASV whereas study of Amin et al considered these in their study and high incidence was proven.

Correlation of bite to ASV administration time and outcome was studied by Narvencar et al, Padhiyar et a with P value <0.0521,16. Significant association ($p<0.05$) was also found in study by Mukherjee et al between time of AVS administration and development of ARF22. In our study where we considered bite to ASV time of 6 hours or less as early administration the outcome in both groups in terms of complications showed statistically significant difference (P value - 0.005). Also, early ASV in our study showed less duration of stay in hospital as compared with people

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administered late ASV and the mean duration of stay in hospital was 11.8 days for early ASV administration and 13.3 for late ASV administration.

31.7 % of patients had AKI. These patients were treated with adequate IVF an ASV. In spite of treatment 46.1% of patients underwent hemodialysis, Table 19 shows other Indian studies that showed similar incidence of AKI is by Dharod M V Patil et al which shows 30.9623 and one more study which showed a lesser incidence than ours is by L H et al which shows 14.6% developed AKI24 whereas the study by Mukhyopaddhay et al showed incidence of AKI as 44.13%, 33.07% underwent hemodialysis25 and Patil et al studied 20.48% of patients having AKI and 52.59% of those undergoing hemodialysis. Maximum viper bites cause high AKI cases.

The varying incidence is probably because of the sample size and the time duration of study and the delay in presentation to hospital after bite that is again attributed to so any social factors. INR was studied on the day of bite in 48 patients and it was found that 18 patients (37.5%) had altered INR (>1.5), similar study in our institute by harshavardhan et al showed high INR in 48% cases26 and a Korean study by Kim J S showed incidence of 52% in their study table 20 27.

FFP was considered in our study when Patients had bleeding manifestation or INR >2 or when required fasciotomy and had thrombocytopenia and high INR.

Studies on compartment syndrome following snake bite are not available although few cases have been reported. Our patients with cellulitis were monitored for compartment syndrome and compartment pressure was measured as mentioned in quick reference guide of 2016 by government of India when clinically it was suspected to be a case of compartment syndrome. Cases of post snake bite compartment syndrome are reported as one by Dinesh Dhar where Patient was taken up for early fasciotomy on clinical grounds28, case report by D K Thomas et al mentioned early fasciotomy and debridement in their case within one hour of presentation 29 whereas small study by Jessica et al insist to measure compartment pressure before faciotomy, the animal model-based study by Tanen D A et al say that faciotomy may worsen the myoencrosis30. Different studies and articles come out with different opinions, but there has been no major study sufficient to support their recommendations. Our study we measured compartment pressure in 13 suspected cases of compartment and did fasciotomy in 10 Patients. Our cut off for compartment pressure was 30 mmHg, Patients with pressure 30 mmHg and above these was subjected to fasciotomy. Like mentioned in study of Gregory juckett et al31 our study also recommends avoidance of prophylactic fasciotomy. Dreaded reason for fasciotomy is myonecrosis due to raise compartment pressure which could be due to the venom itself so prophylactic fasciotomy should not be done unless the compartment pressure is measured when we can attribute the cause to be compartment syndrome and fasciotomy puts the patient open to source of infections and long days of recovery and hospital stay.

Limitation:

Our study had a small sample size. Effect of comorbidities was not studied due to negligible percentage of patients having co morbidities. Traditional treatment taken before approaching could have affected the WBCT readings.

CONCLUSION:

Early and cautious use of ASV influences the outcome in snake bite cases, complications and the duration of hospital stay. Compartment pressure should be measured before fasciotomy to avoid the patient from being subjected to fasciotomy which is done prophylactically in most of the cases or on basis of clinical features of compartment syndrome. In all Patients irrespective of bleeding manifestation investigation for coagulopathy and RFT should be done with strict monitoring of urine output keeping in mind AKI and coagulopathy as common manifestation of viper envenomation. Patients are not aware of importance ASV administration and still do opt for herbal care as first option and then approach primary health centers from where they are referred, unknowingly for which they have to pay huge amount by being hospitalized for long duration of treatment.

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TABLES AND FIGURES

TABLE 1

Table:1 Comparison of WBCT before and After ASV administration among study patients using McNemar's Test

WBCT	Before ASV		After ASV		P-Value
	N	%	n	%	
< 20 min	16	39.0%	37	90.2%	<0.001*
>20 min	25	61.0%	4	9.8%	

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TABLE 2

Table:2 Comparison of Fasciotomy & Disability based on the Compartment Pressure [> 30 mmHg] among study patients using Chi Square Test

Variables	Category	Yes		No		Total		^{2} Value	P-Value
		n	%	N	%	n	%		
Fasciotomy	Yes	10	76.9%	3	23.1%	13	27.1%	30.677	<0.001*
	No	0	0.0%	35	100.0%	35	72.9%		
Disability	Yes	0	0.0%	1	100.0%	1	2.1%	0.269	0.60
	No	10	21.3%	37	78.7%	47	97.9%		

TABLE 3

Table:3 Distribution of Coagulopathy [INR status] among study patients b/w different time intervals using Cochran's Q Test

(HIGH INR >1.5)

Time	INR	n	%	Cochran's Q Value	P-value
Day 1	High	18	37.5%	43.947	<0.001*
	Normal	30	62.5%		
Day 2	High	4	8.3%		
	Normal	44	91.7%		
Day 3	High	1	2.1%		
	Normal	47	97.9%		
Day 4	High	0	0.0%		
	Normal	48	100.0%		

TABLE 4

Table:4 Comparison of mean Hospital stay (in no. of days) based on the time of ASV administration using Kruskal Wallis Test followed by Mann Whitney post hoc analysis

ASV	N	Mean	SD	Min	Max	P-Value	Sig. Diff	P-Value
Early	32	11.8	10.6	1	45	0.003*	Early vs. Late	0.81
Late	9	13.3	13.8	3	45		Early Vs. Not done	0.001*

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Not Done	7	1.9	2.3	1	7		Late Vs. Not done	0.003*

TABLE 5

Table:5 Comparison of distribution of outcomes following ASV administration among the study patients using Chi Square Test

Outcomes	Early		Late		Not Done		χ^2 Value	P-Value
	N	%	n	%	n	%		
None / Dry Bite	0	0.0%	0	0.0%	7	100.0%	31.373	0.005*
Cellulitis Only	8	29.6%	2	22.2%	0	0.0%		
Cellulitis + Coagulopathy	2	7.4%	1	11.1%	0	0.0%		
Cellulitis + Other complications	8	29.6%	2	22.2%	0	0.0%		
Compartment Syndrome only	2	7.4%	1	11.1%	0	0.0%		
Compartment sydrome + coagulopathy	6	22.2%	1	11.1%	0	0.0%		
Compartment syndrome + other complications	1	3.7%	1	11.1%	0	0.0%		
Coagulopathy only	0	0.0%	1	11.1%	0	0.0%		

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