Journal of Cardiovascular Disease Research
ISSN: 0975-3583,0976-2833 VOL13,ISSUE07,2022

# A STUDY OF COAGULATION PROFILE AS PROGNOSTIC MARKER IN PATIENTS ADMITTED FOR SNAKE ENVENOMATION IN THE TERTIARY CARE HOSPITAL OF MANDYA

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## ABSTRACT

INTRODUCTION: Haematological complications are more common than any other complications due to snake bite. Early recognition of signs of envenomation and derangement of haematological parameters can reduce morbidity and mortality. To make more meaningful use of resources such as ASV, Mechanical ventilation and renal support system in patients with snake envenomation,it is important that the health care providers aptly identify those at high risk of potentially fatal complications.

**OBJECTIVES:**To assess clinical and coagulation profiles following snake bite and to analyse the time interval between the snake bite and onset of coagulation profile abnormalities.

**METHOD**: This Hospital-based Prospective observational study conducted in Mandya Institute of Medical Sciences, Mandya was done from January 2019 to December 2019 involving 80 patients admitted following snake bite ,with signs of envenomation . Primarily evaluated with 20 minute clotting time .Information regarding lab parameters like CBC with platelet count ,Prothrombin time, INR, APTT and Bleeding timewere considered. SPSS V22 was used for statistical analysis. P

<0.05 was considered as statistically significant.

**RESULTS:**

Among 80 patients with signs of snake bite envenomation, 77.5% of the patients had prolonged whole blood clotting time (>20 minutes), PT-INR was prolonged (>1.2 seconds) in 66.8% patients and APTT was prolonged (>28 seconds) in 44 (86.2%) of patients and thrombocytopenia (platelet count <1.5 lakh) was found in 13 (26.9%) patients. Bite to needle time >4 hours had increased risk of in-hospitalmortality. Acute renal failure was the commonest complication observed. An in- hospital mortality of 3.75% was observed in the present study.

**CONCLUSION :**It is important to recognize the signs of envenomation and monitor the coagulation profile to treat snake bite patients at the earliest and thus to avoid haematological complications**.**

**KEY WORDS :**Snake bite, Signs of Envenomation, Haematological profile, PT, APTT, WBCT

## INTRODUCTION

Snake bite is a major health problem in India due to prevailing climatic conditions and the fact that major portions of population are rural and agrarians. Envenoming by snakes is an occupational health hazard often faced by farmers and farm laborers of tropical and subtropical countries like India.Most snakebites occur in developing countries with temperate and tropical climates in which populations subsist on agriculture and fishing. Recent estimates indicate that somewhere between 1.2 million and 5.5 million snakebites occur worldwide each year, with 421,000–1,841,000 envenomations and 20,000–94,000 deaths. The true incidence of snakebites is difficult to estimate and often it isunderreported.[1]

Many of the toxins in snake venom interact with clotting mechanism and fibrinolytic system and causes coagulopathy. Disseminated intravascular coagulation can result in serious life threatening systemic complications like hemorrhage, infarction and even death if the treatment is delayed[2]. The effect of cobra bite kills the patients within minutes to hours . In the case of viper bites, which are more common, death occurs over days. Even in the absence of death, the morbidity is high. These factors

necessitate aggressive and specific treatment. Early administration of appropriate anti-snake venom is the specific treatment in snake envenomation.. The correction of coagulopathy is the most important criteria of ASV treatment.

Classification of Snakes based on the type and action of the venom include **ELAPIDS:** Elapids consists of King Cobra, Coral Snake, Common Krait, Cobra and BandedKrait

I. **VIPERIDAE :** It has two different sub families ; Pit Viper – Rattlesnake and the Pit less Viper – Russell's & SawScaled

II. **HYDROPHIDAE**

This contais sea snakes and can be found in the coastal localities.

**Hemotoxicity:** Hypofibrinogenemia and DIC are the main reason for coagulation of blood and is the salient feature of systemic envenomation in wide spread geographical areas. Clinically, features of defective hemostasis include bleeding from the bite site and from cannula puncture sites, at other area of wound and from partially healed injuries in the body.[3,4] Common manifestations of spontaneous systemic bleeding includes, hematuria, gastrointestinal bleeding (hematemesis and melena), gingival bleeding, hemoptysis and cutaneous bleeding in the form of purpura and ecchymosis. Less common are menorrhagia and Central Nervous System bleeding. Subarachnoid hemorrhages / Intracranial hemorrhanges are most important reason for death. Pituitary and adrenal hemorrhage has also been reported. Bleeding may be prolonged and last as long as 26 days or more.[5]Other important feature is (DIC) which may either manifest as bleeding or thrombosis, with resultant ischemia. Intravascular hemolysis may also occur and result in hemoglobinuria and jaundice if it is massive. Hemotoxicity is said to be present if the patient's bleeding time is more than 8 minutes, prothrombin time more than 16seconds or the clotting time more than 30 minutes or if there is abnormal lysis ofclot.

**Neurotoxicity:** Confined to cobra, krait and sea snake bites, the symptoms of neurotoxicity appear from 20 minutes to 15 hours of the bite. According to the extent of envenomation, the symptoms may progress insidiously or rapidly to coma. Ptosis, varying degrees of ophthalmoplegia, palatal palsy, and pharyngeal paralysis with dysphagia, dysphonia, respiratory paralysis and flaccid limb paralysis are the common presentations with the advent of respiratory paralysis, hyoxaemia, drowsiness, convulsions and coma can ensue. The symptoms may progress slowly or fastly to coma depending upon the envenomation spread.

**Nephrotoxicity**[6,7]: In victims with Acute Kidney Injury, oliguria / anuria frequently& quickly develops within the one day, but may be delayed till 48 to 72 hours after the snake bite. Few will have anuria, and rarelynonoliguric.

**Cardiotoxicity of snake venom[8,9]:** Cardiac complications are usually not a prominent feature. They are due to a direct acting cardio toxin where in the symptoms appear rapidly within 30 minutes to 2 hours. It has been reported to occur with both viper and elapid bites. Sudden hypotension, cardiac arrhythmias, cardiac arrest, peripheral circulatory failure and pulmonary oedema are the common clinical manifestations.

**Myotoxicity:** Clinical reports indicate that, in humans, the main invalidating effect is the irreversible disruption of muscle tissue. Tissue necrosis is a relevant local effect caused after snakebites, it is considered as a serious consequence in severe cases of envenomation. When myonecrosis appears tissues are altered leading to the gangrene and infections. This type of complication can be the cause of amputation. Indeed, myotoxins of snake venoms affect mainly the plasma membrane of muscle cells to which they bind through their cationic sequence molecular mechanism by which they caused the muscle tissue damage is not yet fully elucidated. Myonecrosis is due to the myotoxins that induce irreversible damage of skeletal muscle fibres.

bite.

**Chronic complications**

Below complications may occur after snake bite

1. Tissue loss following infection andsloughing
2. Surgical wound debridement of the bitesite
3. Amputation of affectedpart
4. Chronic non healingulcer
5. Bone Infections[Osteomyelitis]
6. Neoplastic conversion might happened due to non-healing skinulcer.

**Snake Bite Management**

World Health Organization along with S.E.A.R.O have released a protocol for the approach and management for snakebite induced Envenomation[10].

**First Aid**

The goal of first aid is to delay the systemic envenomation and abolish lethal sequealae by early transfer of victim to the medical care centre.

**Hospital Management**

In the emergency department, the patient should be assessed for airway, circulation, breathing, and level of consciousness. Immediate attention to be given to patient with shock, respiratory failure, and with altered sensorium/unconsciousness. O2 is mandatory to all patients with envenomation. IV access with wide bored cannula is also important. Isotonic fluid like RL/NS should be infused to prevent shock.

**Anti snake Venom**

Anti snake venom is the specific antidote for venom of snakes. It is an immunoglobulin derived from immunized equine serum.

**Indications For ASV[11]**

Antivenom therapy is indicated with every patient who shows severe systemic and local toxicities. ASV administration is associated with high chances of adverse reactions. It is costly and is not very well available in many areas, so pros and cons to be weighed before initiation oftreatment.

**Supportive Treatment**

The Patient, who envenomed severely, should be admitted in Intensive Care Unit. Patients who envenomed severely can be identified by symptoms such as coma, respiratory paralysis, hypotension, pulmonary edema or syncope.

**Management for Coagulopathy[12]**

ASV plays crucial role in the correction of Coagulopathy. Once ASV has given Coagulopathy immediately reverses. In unique cases with severe uncontrolled bleeding, the following can be given to reverse the Coagulopathy.

1. Fresh wholeblood
2. Cryoprecipitate
3. Fresh frozenplasma
4. Plateletconcentrates

**Management for Renal Failure [13]**

Renal failure is more common in victims who are envenomed with viperiade family. Renal perfusion can be improved by IV fluids – Isotonic saline, Diuretics – Furosemide (up to 100 milligram) or Dopamine – 2 microgram per Kg per minute.

**Management for Neurotoxicity**[14]

Even though antivenom therapy is indicated, patient with bulbar palsy as well as respiratory failure should be given other line of treatment. The patients with symptoms of neurotoxicity should be intubated and supported with mechanical ventilation. The Neurotoxins affects the Myoneural junction and its activity. Its activity is reversed by Anticholinesterase [Neostigmine] and Atropine.

**Management of cellulitis**[15]

Tetanus Toxoid, limb elevation and immobilization ,broad spectrum of antimicrobial agents which covers gram positive and gram negative organisms and anaerobic agent and Fasciotomy should be considered with the development of compartment syndrome.

## METHODOLOGY

A Prospective observational study conducted at Department of General Medicine, Mandya Institute of Medical Sciences, Mandya over a period of 1 year (January 2019 to December 2019) with a sample size of 80.

**Sampling Method :**All the patients who are admitted following snake bite ,with signs of envenomation giving consent to participate in the study and fulfill the inclusion & exclusion criteria will bestudied.

**Method of Collection of Data:** Patient with definitive evidence of venomous snake bite were considered for the study. Primarily evaluated with 20 minute clotting time ; later information including historory of bite, symptoms, signs and lab parameters like CBC with platelet count ,Prothrombin time, INR, APTT and Bleeding time were considered.

**Plan for data analysis:** Data entered using Microsoft Excel software. Analysis was done using descriptive statistics like proportions. Inferential statistics like chi-square test for association, t test, etc, and other relevant statistical tests was used.

**Inclusion Criteria:** Patients admitted following snake bite, with signs of envenomation was included in the study after obtaining informed consent from allpatients.

**Exclusion Criteria;** Patients with pre existing coagulopathy and patients on anticoagulants and antiplatelet drugs were excluded.

## RESULTS AND INTERPRETATION

A total of 80 patients are taken, on admission to Mandya Institute of Medical Sciences, Mandya. They included 54 males and 26 females.

**Figure 1: Graph showing Distribution of Local Manifestation of envenomation**

Among 80 patients , 76 patients experienced pain followed by swelling (75) and cellulitis (75) .

| **FREQUENCY OF SYSTEMIC FEATURES** | | |
|---|---|---|
| **SYSTEMIC FEATURES** | **PERCENTAGE** | **COUNT** |
| No feature | 63.75 | 51 |
| Bleeding Gum | 7.5 | 6 |
| Bleeding from site | 20 | 16 |
| Hemeturia | 3.75 | 3 |
| Epistaxis | 4 | 2 |
| Hemoptysis | 1.25 | 1 |
| Petechia,Ecchymosis | 1.25 | 1 |

**Table 1 : Distribution of frequency of systemic bleeding manifestations**

16 patients developed bleeding from bite site, followed by 6 patients developed bleeding gum and 2 developed nasal bleeding. 3 patients presented with hematuria.

| | **Renal Failure** | **Dialysis** | **ASV Reaction** | **Mortality** |
|---|---|---|---|---|
| No | 70 | 76 | 70 | 77 |
| Yes | 10 | 4 | 10 | 3 |

**Table 2: Distribution of frequency of Complications**

Out of 80 patients renal failure was seen in 10 patients in which 4 of them had to undergo dialysis. Reactions to ASV occurred in 10 individuals which was treated with 0.1% adrenaline and steroids. Mortality occurred due to renal failure, sepsis, septic shock or DIC. Mortality rate was around3.75%.

**Figure 2: Graph showing Distribution of frequency of Renal failure**

**Figure 3: Graph showing Distribution of Clotting time prolongation**

20 minute whole blood clotting time was prolonged in 77.5% of our study population.

| **PROLONGED PT -INR(>1.2)** | | **PROLONGED APTT(>28 S)** | | **THROMBOCYTOPENIA** | |
|---|---|---|---|---|---|
| YES | NO | YES | NO | YES | NO |
| 66.8 | 43.2 | 86.2 | 23.8 | 26.9 | 73.1 |

**Table 3: Distribution of abnormal coagulation parameters**

**Figure 4 : Graph showing Distrition of abnormal coagulation parameters**

PT-INR was prolonged (>1.2 seconds) in 66.8% patients and APTT was prolonged (>28 seconds) in 86.2%of patients and thrombocytopenia (platelet count <1.5 lakh) was found in 26.9%patients.

| **AVERAGE PROTHROMBIN & AVERAGE ACTIVATED PARTIAL THROMBO PLASTIN ACROSS GRADE BITE** | | |
|---|---|---|
| **GRADE** | **AVERAGE PROTHROMBINTIME** | **AVERAGE ACTIVATED PARTIAL THROMBO PLASTINTIME** |
| **G1** | **13** | 32.35 |
| **G2** | **20.78** | 51.7 |
| **G3** | **23.71** | 71.79 |

**Table 4: showing Comparison of Average prothrombin time and Activated partial thromboplastin time with Grade of bite**

**Figure 5: Graph showing Comparison of Average prothrombin time and Activated partial thromboplastin time with Grade of bite**

Average prothrombin time in Grade 1 was 13 , Grade 2 it was 20.78 , Grade 3 it was 23.71

| **MORTALITY** | |
|---|---|
| **EXPIRED** | **RECOVERED** |
| 0 | 43 |
| 1 | 22 |
| 2 | 12 |

**Table 5 :Frequency Distribution of clinical outcome of Snake bite**

Out of 80 patients only 3 patients succumbed and 77 patients recovered.

| **MORTALITY ACROSS GRADE BITES** | | |
|---|---|---|
| **COUNT** | | |
| **GRADE** | **MORTALITY** | |
| | **EXPIRED** | **RECOVERED** |

| | | |
|---|---|---|
| G1 | 0 | 43 |
| G2 | 1 | 22 |
| G3 | 2 | 12 |

**Table 6: showing Comparison of Mortality with Grade of bite**

In our study 3.75 % was the mortality rate and happened in grade2 and 3 patients only due to DIC, acute renal failure, refractory shock and/or severe sepsis .
Chi-square p-value = 0.04 ( significant)

| **DURATION OF STAY IN WARD(DAYS) ACROSS GRADE BITES** | | | | |
|---|---|---|---|---|
| **Count** | | | | |
| **GRADE** | **DURATION OF STAY IN WARD(DAYS)** | | | |
| | **1-2** | **3-4** | **5-6** | **7 & above** |
| G1 | 31 | 3 | 9 | 0 |
| G2 | 7 | 13 | 2 | 1 |
| G3 | 2 | 4 | 2 | 6 |

**Table 7:showing Comparison of duration of hospital stay with grade of bite**

Majority of patients stayed in the hospital for 1 to 2 days and only 7 Patients stayed in the ward more than7 days. Majority of Grade 3 snake bite patients stayed for more than 7 days. Chi-square p-value = 0.004 (significant)

## DISCUSSION

The current study is a Prospective observational study and included 80 patients who are admitted following snake bite ,with definitive evidence of envenomation.

Eighty snake bite patients admitted in our hospital were included in present study. Among them, 54 were male and 26 female. patient gender ratio being around 3:1.Signs of inflammation due to envenomation in the present study were 95% which is comparable with Athappan et al[16](98). In the present study pain was the most common local manifestation , noted in 95% of the cases, 93% cases showed swelling, similar to Mishra's series[17] (100%) and Sarangi'sseries[18]

(84%). In our study we noticed that 8 of our patient with haematological toxicity did not have cellulitis. 5 of them were admitted within 4 hours after bite. This may be due to delayed systemic absorption of venom, less local effect of venom ,or early neutralization of venom by ASV (Jacob et al).

In our study bleeding manifestations were present in 27.25% and absent in 63.75%. Gum bleeding was present in 7.5% , Bleeding from site present in 20% of individuals . According to Patil et al. gum bleeding was found in 7 (7.95%) patients with vasculotoxic snake-bite with DIC. Total 9 (10.22%) patients had hematuria and 5 (5.68%) patients had hematemesis. Complications like renal failure was seen in 10 out of 80 patients in which 4 of them had to undergo dialysis. Reactions to ASV occurred in 10 individuals which was treated with 0.1% adrenaline and steroids. Mortality occurred due to renal failure, sepsis, septic shock or DIC. Mortality rate was around3.75%.

The incidence of Acute Renal Filure in study by srilatha et al[19] was 34% and chugh et[20] al was 28.8% but in my study it is 12.5%(10 out of 80).Out of 10 patients of ARF, 4 patients had anuric renal failure and 6 had oliguric renal failure. All 4 patients with anuric renal failure, required hemodialysis on a daily basis, 2 of them developed acute pulmonary oedema for which they were being treated with hemodialysis, 1 patient developed hyperkalemia, and the other one developed uremic symptoms. 6 patients of oliguric renal failure were being treated with IV fluids and they responded well. Renal failure and Dialysis were common in grade3.

Clotting time (CT) is the main bedside test to assess the degree of envenomation in vasculotoxic snake bite. Our finding showed that 77.5 % of cases had prolonged clotting time comparable to [83% (30 out of 35) reported by Harshavardhana et al]. WBCT >20 Mins is comparable with the study of Paul J Dasgupta et al[21]. (74%)The criteria for Anti snake venom indications clearly states that ASV should be administrated if there are local signs of envenomation, like cellulitis or lymphadenitis even if clotting time is normal. Reid et al reported 100% cases of definite envenomation exhibited prolongation of clotting time[22] (95% in Odisha study).

PT-INR was prolonged (>1.2 seconds) in 66.8% patients and APTT was prolonged (>28 seconds) in 86.2%of patients and thrombocytopenia (platelet count <1.5 lakh) was found in 26.9% patients.

Most patients in our study had normal bleeding time. Few patients with systemic bleed had only minimally elevated bleeding time, by this finding we were able to come to a conclusion that decreased platelet count was not the major cause of bleeding. Our finding (mean bleeding time 3.42 minutes) is in concordance with Patil et al (3 minutes ). Only 10% of bite cases showed prolonged bleeding time in the study conducted in Orissa[5]. In contrast to 5% reported by Reid etal[7].

Majority of patients clotting time was normalized within 6 hours of ASVadministration . Maximum time for normalization of clotting time in our study was around 24 hours. It was highly dependent on the degree of envenomation. Average Dosage requirement of ASV was around 13 (6 to 30) vials (same as Biradar et al). Reid et al reported that the clotting time returned to normal in 9 hours with specific antiserum, and 24 hours with polyvalent serum. Our study used fixed adequate dose of polyvalent serum alone. Development of complications and normalisation of clotting time were both dependent on degree of envenomation.

Mortality rate in our study 3.75 % was the mortality rate and happened in grade2 and 3 patients only due to DIC, acute renal failure, refractory shock and/or severe sepsis (leading to septic shock). Only 2 deaths out of 88 vasculotoxic snake bites were reported by Patil et al, (2.27%) one with severe ARF and another with CVT plus ARF plus cellulitis, aspiration pneumonitis and septicemia. Case fatality in Harshavardhana et al study was 4% and was mainly due to hypovolemia, intravascular hemolysis, venom induced nephrotoxicity or a syndrome resembling disseminated intravascular coagulation. In Gangadharam et al study the case fatality rate was 3%. Out of 35% of viperine bites, 2 patients died of acute renal failure and another patient developed DIC with ICH .

## CONCLUSION

Mortality and morbidity was higher with severe form of envenomation. Most common complications with hemotoxic snake bite was DIC, renal dysfunction, and cellulitis. DIC was the main mechanism of underlying coagulopathy. . Whole blood clotting time was the main bed side test available for assessing reversal of coagulopathy.Delay in time in presenting to the hospital is one of the valid predictors of poor outcome in snake bite induced coagulopathy.Earlier presentation to hospital decreased both morbidity and mortality.

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