DISSERTATION
ON

A STUDY ON

COAGULATION PROFILE IN SNAKE BITE

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CERTIFICATE

This is to certify that this dissertation titled **" A study on coagulatiotn profile in snake bite "** submitted by **Dr.G.Vasanth** to the faculty of Internal Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D., degree branch I (Internal Medicine) is a bonafide research work carried out by him under my direct supervision and guidance.

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CONTENTS

INTRODUCTION

Snakes are fascinating part of nature. Their colour, movement and secretive habits make them seem more mysterious than other animals. For people interested in wildlife, snakes are a wonderful introduction to the world of nature. There are over 3000 species of snakes in the world, of which more than 200 – ranging in size from 100mm long worm snakes to 6m long pythons – are found in India.[1] Snakes occur in most habitats from warm seas to deserts, and from swamps, lakes and farmlands up into the mountains. These predators play a major role in the maintenance of the ecosystem.

India has been known as a land of exotic snakes. Here, snakes have been worshipped as Gods for thousands of years. Even today, in Bathis Shirala, Maharashtra, during the harvest festival called 'Nag Panchmi', freshly caught cobras are worshipped with flowers, ghee and money. Most of us flee at the sight of a snake. However, a group of people have based their living on these primitive reptiles. In south India, the Irula tribals, over years, have been supplying millions of snakes skins for export. As this trade has been banned today, they catch snakes for venom extraction, and this venom is used in the process of anti venom production.

Snakebite is a common emergency encountered in day-to-day practice. Morbidity and mortality due to snakebite is a preventable health hazard

in the tropical and sub-tropical countries. In India, due to the prevailing climactic conditions, due to the fact that a major portion of the population is rural and agrarian, snakebite is a major health problem. Every year, 15,000 die out of 2,00,000 snakebites in India. The death rate is approximately 7.5%. However, this figure is based on hospital statistics. whereas in practice, most rural patients prefer treatment by traditionally healers and do not go to hospitals.

Dr. Patrick Russell in 1796 (then aged 69) wrote from India of snakebite: "…… the progress of diseases, and succession of symptoms, had either not been attended to or were indistinctly recollected ……." His plea for the clinical observation remained largely unheeded for years until the landmark study in 1963 by Reid. Since then a number of studies have been carried out.

It is true that the effect of cobra bite kills the patients within minutes to hours – however, if managed sufficiently early with anti-snake venom, the patient recovers soon. 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. The effect of viper bites on the haematological system and their management still holds a lot of controversy. We have chosen a study on these haematological effects and response to treatment as our institute is situated in a primarily rural setting with a high inflow of cases, mainly viper bites.

AIMS OF THE STUDY

1. To assess the changes in coagulation profile following snake bite.
2. To document the species of snakes that commonly cause coagulation abnormality.
3. To study the common forms of systemic bleed in snake-bitten individuals.
4. To analyse the time intervals between the snake bite and onset of coagulation profile abnormalities.
5. To correlate the clinical severity to the abnormalities of quantitative coagulation tests.
6. To study the time taken for reversal of changes in coagulation profile to normal following anti-snake venom therapy.
7. To find correlation between coagulation abnormalities, their reversal and the time interval between bite and starting of treatment.
8. To look for the association between renal failure and alteration of coagulation profile.

REVIEW OF LITERATURE

TAXONOMY, IDENTIFICATION AND DISTRIBUTION OF SNAKES

There are about 2500 to 3000 species of snakes of which about 500 belong to the five families of Venomous snakes, Atractaspididae, Elapidae, Hydrophidae, Colubridae [some species] and Viperidae.[4] In India 236 different species of snakes are found out of which 50 species are reported to be poisonous.[2] Among the non-venomous snakes only the giant constrictors are potentially dangerous to man – these include the South African and Asian pythons, and the South American anaconda [4].

Poisonous snakes prevalent in India belong to four families. They are

1. Elapidae – includes cobras & krait
2. Viperidae (true vipers) – includes Russell's viper & saw scaled viper.
3. Colubridae (pit vipers) – includes green pit viper.
4. Hydrophidae (or) sea snakes.[5]

In India, although 50 species belonging to these families are venomous, most are no threat to man. The only venomous snakes to

be wary of are the “Big four” – COBRA, KRAIT, RUSSELL VIPER and SAW SCALED VIPER.[2]

COBRAS: Two species of cobras are found in India, common cobra (Nalla or Nagu Pambu) and king cobra (Raja Nagam or Karu Nagam). Cobras vary in colour from black or dark brown to yellow white[1,5]. The head is indistinct from the neck and the ribs in this region are movable and expand to form the hood. This hood on its dorsal aspect resembles a spectacle showing a connected pair of rings. Cobras are often confused with Indian rat snakes (sara pambu) which have a much thinner neck and head and are about 3 feet longer than India Cobras. King Cobras are found in dense forests and are upto a length of 18 feet. They are usually black in colour.

KRAITS: Two species of Kraits are commonly found in India. Common Krait (kattu viriyan or karuvelan pambu) and Banded krait (pattai kattu viriyan). Common krait is steel blue or black with white bars on the back. Banded krait is larger and is jet black in colour with yellow bars. Kraits are usually found in pairs.

RUSSELL’S VIPER: (KANNADI VIRIYAN) : This is a larger snake measuring 6 feet and is stout, lazy looking and makes a loud hissing sound by expelling air through its large nostrils. It is brown

or yellowish with dark round spots on the dorsum edged with white and black colour.

SAW SCALED VIPER: (SURUTAI PAMBU) : A small snake (30cm long) with brown or grayish dorsum showing zig zag pattern. It has a distinct cross or lance mark on the head. The ventral scales are rough. They produce a rasping sound by rubbing their coils together. This snake is often confused with a non poisonous snake " cat snake" (ponnai or ollai Pambu) which has a thin long tail, prominent eyes and a clear mark on the head. Most often a killed snake is brought by the patient and physician has to identify whether they are poisonous or not. Generally speaking non poisonous snakes have blunt tails, solid teeth, no fangs and semicircular ventral scales. Ventral scales do not completely cover the belly except in colubridae (rat snakes). But if the physician has a mental picture of the four common poisonous snakes it would be much easier for him to know which bite has to be given significance.

RUSSEL VIPER (KANNADI VIRIAN)

KRAIT (KATTU VIRIAN)

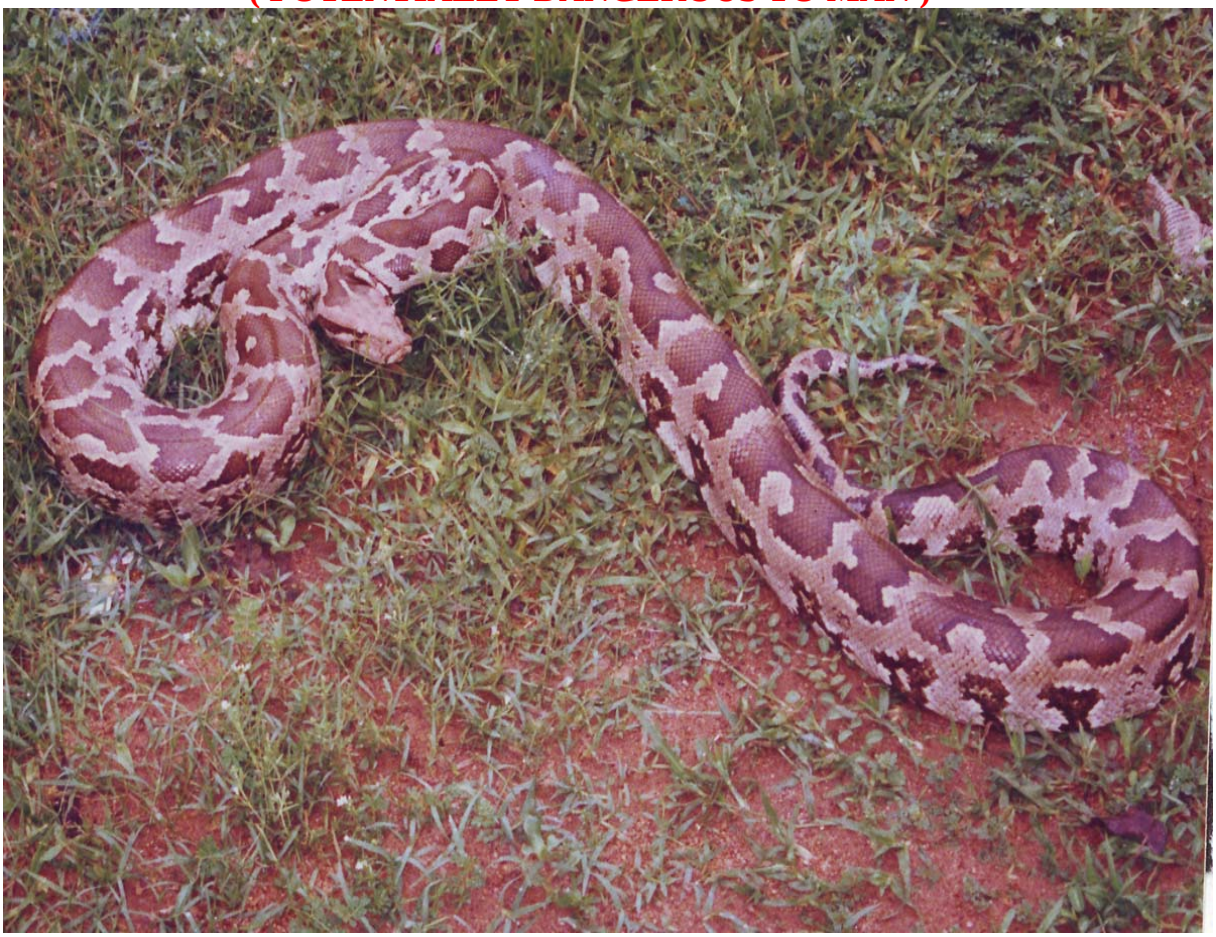
SAW SCALE VIPER (SURUTTAI PAAMBU)

CAT SNAKE (OLAI PAAMBU) (NON POISONOUS)

COBRA (NALLA PAAMBU)

KING COBRA (RAJA NAAGAM)

INDIAN PYTHON (MALAI PAAMBU)
(POTENTIALLY DANGEROUS TO MAN)



GENERAL FACTS ABOUT SNAKES

Snakes are cold blooded animals without ears or tympanic membrances. They react to vibrations received through the surface on which they rest rather than air borne vibrations. Snakes do not have a distinct visual system and they do not readily assocate stationary objects with danger. Their sense of smell is the important. Most land snakes feed on mice, rats and frogs. Kraits and Cobras are exceptional in being mainly snake eaters. No one knows the life span of snakes in the wild. Longevity of some Indian snakes kept in zoos and by individuals include, Indian python : 34 yrs; Banded Kraits:11yrs; Indian cobras 21yrs; saw scaled &Russel viper: 10 yrs; . The south Indian tribals who have based their living on snakes are called 'Irulas'.

Epidemiological Features of Snake Bite

Documented reports of epidemiological studies of snake bite in India are few. Although the exact number of persons inflicted by snake bite is not known, it is estimated that about 2,00,000 persons are annually bitten by snakes in the country and about 15,000 of these are fatal[7] In a study conducted in Tamilnadu, hospital records showed a mortality of 11.6%. According to a study by Sawai in 1974, 71% of the victims are found in the age group of 11-50 yrs and 75% of the victims

were male. A safdarjung Hospital study showed 81.5% of victims to be field workers. 75% bite occurred outdoors; 88.6% of victims were from rural India [6]. Incidence of snake bite in India shows a seasonal variation. In North India 70-80% of bites are seen in the warmer months may to October [6]. while a study conducted in Calicut Medical College, Kerala showed a maxium incidence of complications also maximum during this period.[8]. Sawai's study in 1974 showed 68% of snake bites occurred in the evening and night; 32% in the morning and afternoon. 72% of bites were on the lower limbs; 25% on the hand and arm; and 3% were on the trunk.

VENOM APPARATUS AND COMPOSITION

In certain snakes (poisonous) the paired salivary gland has assumed a very significant function (venom apparatus)[6].They secrete venom, a powerful multipurpose enzyme fluid through the channeled or grooved teeth, the fangs[6]. venom can be injected from the bottom of the fang (viper) or by an opening at the anterior aspect of the fang, a few millimeters above the tip[4]. (performance of the venom apparatus varies with different species)[4]. Palestine vipers in catching their prey inject lethal doses of venom at each of ten or more humans in rapid succession, the second or third victims were sometimes more envenomed than the first[4]. However Russell vipers appear to inject most

of their available venom at first strike[4] . 50% of Malayan pit viper bite showed little or no envenoming. This suggests that some snakes might be capable of biting defensively without injecting venom.

Snake venom is a complex fluid with powerful ingredients that acts to immobilize its prey. Hence snake bite on humans is a mere accident. Venom is faint, transparent, yellowish, slightly viscous and acidic. It is extremely heterogenous containing about 15 enzymes and 10 non enzymatic proteins and peptides and at least a dozen of other substances[6]. Various components of the snake venom have been mentioned in the accompanying table. Deoras in 1965 reported the lethal dose of venoms of common Indian poisonous snakes to be : cobra – 0.12g , Krait- 0.06g, Russell viper-0.15g and Echis carinatus – 0.08g[9a]. Variations in venom composition from species to species explains the varied clinical presentation of snake bite. There is a considerable variation in the relative proportions of different venom constitutions within a single species throughout the geographical distribution, at different seasons of the year, and as a result of aging [4,8] Hyaluronidase is present in almost all snake venoms. It hydrolyzes the hyaluronic acid in interstitial spaces of the cells and connective tissue allowing further penetration of venom into surrounding tissues [6]

Proteases in viper venom activate the mammalian clotting cascade by activation of factor Ix or X. Ecarin a zinc metalloprotein activates prothrombin. [4].

ENZYMATIC EFFECTS OF SNAKE VENOM	
ENZYME	**EFFECTS**
ARGININE ESTER HYDROLASE	Bradikinin release , interference with clotting.
PROTEOLYTIC ENZYMES	Tissue destrucion , some causes bleeding.
COLLAGENASE	Digestion of collagen.
HYALURONIDASE A	Reduction of collagen viscosity.
PHOSPHOLIPIDASE A	Un coupling of oxidative phosphorylation
PHOPHOLIPIDASE B	Hydrolysis of lyso phosphorylation.
PHOSPHODIESTERASE	Inhibition of DNA , RNA , arabinose dreivative.
ACETYL CHOLINESTERASE	Catalysis of hydrolysis of Ach.
5' NUCLEOTIDASE	Specific hydrolysis of mono esterase which links with 5' position of DNA , RNA , L-amino acid oxidase catalysis of amino acid oxidation.
THROMBIN- LIKE ENZYMES	Depression of fibrinogen levels.

NON- ENZYMATIC COMPONENTS IN SNAKE VENOM	
COMPONENT	**EFFECTS**
NEUROTOXIN: Cobra toxin Erabutoxin Alpha bungarotoxin	Poly synaptic non- depolarising neuro muscular nicotinic Ach receptors. To some extent cardio toxic , hemotoxic , and anti coagulant.
CERULOTOXIN: (KRAIT) Beta bungarotoxin	Similar post synaptic block but without binding to receptors. Pre synaptic motor nerve end blockade.
HAEMORRHAGINS: (HR-1 , HR-2) (viperidae , crotolidae)	Direct distruption of vessel endothelium. Pro coagulant effect : Factor IX activation by cleavage of peptide bonds . Factor X activation by calcium binding to gamma glutamic residues in X with rapid change Xa. Direct pro thrombin activation by cleavage of peptide bonds by venom . Anti coagulant effects: by inhibition of platelet , clotting factors and direct fibrinolysis.
CARDIOTOXIN: (Naja naja)	Neuro muscular blockage , hemolysis , cytotoxicity , cardiac arrest.

Phospholipase A2, the most extensively studied of al venom constituents has damaging effect on RBC, platelets, leucocytes, skeletal muscle, Endothelium, presynaptic terminals and also has opiate-like sedative effect.[4].

Polypeptides called neurotoxins also cause presynaptic inhibition by blocking acetylcholine release or post-synaptic inhibition blocking its action.[4]

Haemorrhagins (HR-1 and HR-2) cause disruption of basement membrane of vessels and cause bleeding into organs.[6]

CLINICAL FEATURES:

The clinical features of snake bite can be considered under the following three headings:-

1. Local effects.
2. Systemic effects
3. Complications.

1. Local effects:

The limb bitten by the snake shows increased vascular permeability leading to swelling& bruising. Factors responsible include proteases, phospholipases, hyaluronidase and endogenous autocoids released by the snake venom like histamine and kinin. Venoms of some vipers cause a diffuse increase in vascular permeability causing pulmonary

edema.[4]. Local tissue necrosis occurs as a result of the direct action of myotoxic and cytotoxic factors, ischaemia due to thrombosis, external compression by tight tourniquets or swollen muscles [4]. Regional tender lymphadenitis is an important clinical sign, occurring early, and is toxin mediated. Local swelling is a valuable sign of viper bite to the extent that its absence excludes viper bite [9]. Local swelling occurs rarely with the Asian cobra bite, but is not seen with Krait or sea – snake bites [9].

2. Systemic features

Fear and emotional reactions : Whether the snake is poisonous or non poisonous, fright is a common symptom. Patient may appear semiconscious with cold,. clammy skin, feeble pulse and rapid shallow breathing.[9]

Bleeding and clotting disturbances: These are commonly seen after viper bites. This is due to procoagulant activity leading to consumption coagulopathy, anticoagulant activity inhibiting coagulation factors or due to thromobocytopenia.[4]. In the absence of trauma these generally do not causes spontaneous bleeding. If it occurs it is usually attributed to direct actions of haemorrhagic toxins.[4]. Commonest haemorrhagic manifestation seen in a study done by virmani and dutt in Jammu was haematuria ,while for reid it was hemoptysis [10,11]. Other common types of bleeding include haemetemesis and bleeding from gums, injection

sites, and nose [10] . Discoid ecchymoses have been noted by reid in his studies [11]. A few Australian land snakes can cause haemolysis.[4]

Neurological disturbances: Neurotoxic polypeptides and phospholipases of snake venom cause paralysis by blocking transmission at neuromuscular junctions (post synaptic for krait and cobra, responds to neostigmine).[4,4a]. This is characteristic of kraits, cobras and coral snakes. The early features would be prominent forehead wrinkles, then ptosis, external ophthalmoplegia and finally paralysis of bulbar muscle causing respiratory paralysis[4]. Some patients bitten by elapids or vipers are in a physiologically drowsy state in the absence of respiratory or circulatory failure probably due to release and binding of endogenous opiates.[4]

Rhabdomyalysis : Generalised rhabdomylysis with release of myoglobulin, muscle enzymes and potassium causes respiratory failure, hyperkalemia and occasionally renal failure (mainly seen in sea-snakes).[4]

3. Complications

(i) Hypotension/shock: The cause of shock following snake bite include

- Pain shock due to vasovagal mechanisms.

- Vasodilating autocoids and oligopeptides in viper venom inhibit the kininase enzyme leading to vasodilatation and shock
- Life – threatening anaphylactic reactions in previously sensitised individuals within minutes of being bitten.
- Hypovalemia from loss of blood and plasma into swollen limb or massive gastro intestinal hemorrhage.
- Direct myocardial action of toxin can contribute to hypotension (cardiogenic shock).
- Pulmonary edema due to multiple effects (myocardial failure, increased permeability of pulmonary vessels) also contributes to shock.

ii. Renal Failure:

` Ischemia (due to hypotension and DIC), nephrotoxic effect of venom, pigment nephropathy associated with rhabdomyolysis and intravascular haemolysis contribute to the development of acute tubular necrosis, bilateral cortical necrosis and renal failure commonly seen with Russell viper.[12]. It is the commonest cause of mortality in viper bite.[6]

Iii. Gangrene/necrosis:

It is reported to be of high incidence in the United States of America and Japan following snake bite, but is rare in India.[6]

PRINCIPAL FEATURES OF ENVENOMATION BY DIFFERENT FAMILIES OF SNAKES

- **E**lapidae (krait / cobra) - principal manifestation is neurotoxity. Local blisters and necrosis can occur. Australian Elapides cause bleeding manifestation.[4]
- **V**iperidae (Russell viper / Saw scaled viper) - local swelling, cellulitis, regional lymphadenitis and bleeding manifestations.[4]
- **H**yperphiidae (sea snake) – Rhabdomyolysis [4].
- **C**olubridae : Bleeding manifestation and renal failure.[4].

INVESTIGATIONS IN A CASE OF SNAKE BITE

1. Clotting Time: Incoagulable blood is a cardinal sign of systemic envenomation by majority of vipers. For clinical purposes a simple all or nothing test of blood coagulablity is adequate [4]. A few milliliters of blood taken by venepuncture are placed in a clean dry test tube.[4]. More sensitive tests like prothrombin time and Fibrin Degradation products are not used routinely and are indicated only in special situations.[4]. Though snake bite is associated with thrombocytopenia, platelet count is not routinely needed until patient develops bleeding.

2. Blood Urea , Serum Creatinine and Electrolytes are indicated to detect development of Renal failure.[4]

3.Urine Examination for red blood cells.[4].

4.White Blood cell count – Leucocytosis above 20,000 indicates severe envenomation

5.Packed cell volume is done if patient develops bleeding.

6.Additional Investigations: Done only in specific conditions.

- Rhabdomyolysis (Sea Snake) – Rise in myoglobulin and creatine phosphokinase.
- Renal failure – PH, PCo2, Bicarbonate estimation,urine sodium
- Shock (Cardiotoxin) – Electrocardiogram.
- Pulmonary Edema – Chest X-ray.

IMMUNO DIAGNOSIS

Enzyme linked immunosorbent assay is a very important tool for studying both the epidemiological and clinical effects of snake bite in humans. In places where specific anti snake venom is available against each species, if the snake is not brought along with the victim for identification, immuno detection of specific snake venom antigen in body fluids of the patient will help in management.[12] It has

been proved by ELISA that effects of envenomation depend up on hours (i.e, blood venom level x time elapsed between bite and institution of treatment) rather than blood level of venom.[13]. Immuno diagnosis kits are unlikely to be of practical help unless their present cost is substantially reduced and speed of diagnosis is increased [14]. Studies in Liverpool are in progress to increase the rapidity of assay to provide specific diagnosis within 10 minutes of sampling [12].. ELISA by detection of snake venom antibody can be used for retrospective diagnosis of envenoming in epidemiological studies.[14].

GRADING

Grading of the effects of viper bite has been done by different authors in varying patterns. The grading used by Reid in his study included both local and systemic effects in grading bites as those with nil, mild, moderate and severe emvenomation.[11]. In an Indian study this grading system was found to be complex and not very useful.

A much simpler manner of grading would be:-

Nil – no local cellulites \ lymphadenitis ; CT normal

Grade I – local cellulites + regional adenitis; CT normal

Grade II – CT prolonged +/- local signs

Grade III – CT prolonged + systemic features like bleeding and shock.[15].

MANAGEMENT

General Measures:

- Reassure the victim [4]
- Immobilize the bitten limb using a splint or sling
- Cauterization, incision and drainage, amputation, usage of venom pumps, instillation of chemical compounds and electric shock locally are all to be avoided as these will cause uncontrolled bleeding from the site and damage of nerves and vessels, leading to necrosis.[4].
- Use of tourniquets are controversial, dangers of their application include ischemia and gangrene, damage to peripheral nerves and increased local effect of venom. But in case of cobra or sea snake if medical therapy is likely to be delayed a firm crepe bandage can be applied.
- Inj. Tetanus toxoid should be given.

Specific therapy:

ANTISNAKE VENOM THERAPY

INDICATIONS:

Distinction of poisonous from non-poisonous snake is often difficult, and is not usually important for the clinician. It is known that about 15 drops

of viper venom can be fatal to an adult and 3 drops of cobra venom could be lethal, and that one drop of sea snake could kill 5 men. Fortunately human bite is a defensive reaction which rarely results in much venom being injected. Following poisonous snake bite more than half of victims will have minimal or no poisoning. Hence poisonous snake bite is not synonymous with snake bite poisoning. So even though the snake is identified as poisonous. Or there are bite marks, treatment should be given only if there are signs of envenomation. Antisnake venom itself can be fatal and it is a costly drug with limited supply.[9]

CLINICAL INDICATIONS

- Hemostatic abnormalities
- Neurotoxicity
- Generalized rhabdomyolysis
- Definite evidence of local envenomation.

CONTRAINDICATIONS:

There is no definite contraindication as Anti snake venom is the only specific therapy for snake bite. Atopic patients and those who had reaction to equine antiserum on previous occasions

have an increased risk of developing severe antivenom reactions. It can be ameliorated by pre-treatment with adrenaline, anti-histamine and corticosteroid.[4]

TYPES OF ANTI SNAKE VENOM:

Mono – specific forms are more effective and less likely to cause reactions than polyspecific antivenom. In most developing countries only a single polyspecific antivenom is available[14]. In India ASV is produced by Haffkine Institute, Bombay, and Central Research Institute, Kasauli. It is produced by hyperimmunizing horses against the common four poisionous snake (Cobra, Krait, Russell's and Saw scaled viper).[1]

DOSE OF ANTI- VENOM:

The dose schedule for polyvalent and monovalent antisnake venom varies. We know the lethal dose of Cobra is 0.12g, Krait – 0.06g, Russell viper – 0.15g, Echis carinatus- 0.08g. Poly valent anti- snake venom 1 ml neutratilses 0.6mg of cobra venom, 0.45mg of Krait, 0.6mg Russell viper and 0.45mg of Saw Scaled viper venom. Based on this if the poisonous snake is known , dose of anti snake venom can be estimated theoretically. But practically it is not applicable as amount of venom injected in each patient and by each bite varies. And invitro studies do not correlate with invivo results.

Based on the results of a number of studies the dose of anti snake venom conventionally recommended as initial dose if snake is known is : common krait – 100ml of Haffkine polyspecific antivenom; Russell viper -100ml, Indian Cobra -100ml and Echis Carinatus -100ml.[4]. If the snake is not known the recommended amount of anti snake venom given based on clinical signs is 50ml, 100ml, and 150ml for grades I to III. For patients presenting with neurotoxic features initial dose of ASV given in 100ml.[15].

The apparent serum half-life of antisnake venom in envenomated patients ranges from 26 to 95 hours depending on how they are prepared[4] .Though it clears the venom from the circulation immediately, the clinical effect on clotting restoration occurs usually after four hours. Thus if dose has been adequate clotting time should be normal by 6 hrs [4,16].. Neurotoxic signs improve within 30 mins but may take several hours. A second dose is given if neurological features persist for more than 30 minutes. Dose of ASV is the same for adults and children.[4]

There is controversy about how long after envenomation Anti – venom therapy is still effective. Carrison et al claim that it is most useful if given within 4hrs, less if delayed for 8 hrs, and doubtful if given after 24hrs [17] However, Dwivedi et al have reported therapy with anti-

snake venom to be beneficial even after 8 days and state that there is no fixed time limit.[18].

MODE OF ADMINISTRATION:

Local Injection: If it were possible to inject anti-venom locally at the site of bite within a few minutes, necrosis might well be prevented. But in practice this is virtually never possible and therefore is not advocated.[9]

Intravenous injection: It is the most effective route. An infusion of anti-snake venom mixed with isotonic fluid is given in 1:3 dilution. It is given over 30-60 minutes, initially starting with 10-15 dps/mt and then increasing the dose [4]. ASV can also be given direct intravenous bolus. It was found there is no difference in reaction between the two methods.[19]

ANTIVENOM REACTIONS AND TESTDOSE

Anti snake venom therapy is complicated by 3 types of reaction. 1. Early (Anaphylactic), 2. Pyrogenic, 3. Late Serum sickness type reaction.

Early anaphylactic reaction was initially thought to be IgE mediated. However, in most there is no prior exposure to serum. Skin test dose reactions do not correlate with the incidence of reactions occurring during ASV administration.[4,19] Complement activation is also implicated, but not proved.[19] Clinical features include itching, utricaria, fever, tachycardia, palpitations, nausea, and vomiting. Early reactions are managed by 0.5ml of 0.1% adrenaline sub cutaneous and chlorpherneramine malete 10mgIV.[4]. Pyrogenic reactions results from contamination of anti- snake venom with endotoxin like compounds. High fever occurs which is treated with paracetomol.[4]

Late serum sickness reaction develops 5-24 days later, characterized by fever, itching, urticaria, arthalgia and lymphadenopathy, and is treated with chlorpheneramine 2mg four times daily or prednisolone 5 mg four times daily for 5 days.[4].

The role of the intra dermal test with 0.2ml of ASV, though widely followed, is controversial. According to some authors, this test only delays the onset of definite therapy and has no role in the prediction of early or late Anti- snake venom reactions.[4,19]

Other supportive measures

- Neurotoxic effects – Artificial Ventilation.

Intravenous neostigmine 0.5mg given at half hourly interval for five injections. This is followed by same dose at increasing intervals of 2 to 12 hours according to neurological recovery. Each dose of neotigmine is preceded by 0.6g atropine [6] . Shock- Plasma Expanders, Dopamine infusion, Steriods are used.[4].

- Renal Failure – During initial oliguric phase (less than 400ml/24hrs) dopamine infusion at the rate of 2.5microgr/kg/minute or diuretics are used. In established renal failure, dialysis is indicated.[4].
- Local infection: Intra compartmental syndrome – broad spectrum antibiotics are used. Blisters are best left undisturbed. Slough should be excised. Swelling of muscles within tight fascial compartments may raise the tissue pressure leading to impaired perfusion and ischemia. In these circumstances fasciotomy is indicated. It should be done only after blood coagulopathy has been treated.
- Steroids are advocated in both patients presenting with bleeding tendencies with neurological manifestations (Hydrocortisone 50 to 100mg I.V 8^{th} hrly). However, its use remains controversial.[20].
- Heparin : Some studies show that if heparin 10,000 units is given intra venously stratum followed by 5000 units 8^{th} hrly IV and

continued for 48 hrs it is useful in the prevention of DIC.[21] Yet, other studies have shown it to be ineffective and worsening bleeding.[14].

- Fibrinogen infusions are not helpful.[14]
- Blood Transfusion: Helps in viper bite shock secondary to bleeding and also helps in the management if specific antivenin is not available.

HEMORRHAGIC AND BLOOD COAGULATION DISTURBING ACTIONS OF SNAKE VENOM.

HISTORICAL REVIEW:

The effect of snake bite are of two main kinds neurotoxic and hemorrhagic. In the course of history people have been impressed by the dramatically rapid lethal action of neurotoxic venoms, classically illustrated by Cloepatra's suicide. Hemorrhagic effects of snake bite have also been known for thousands of years. Two hemorrhagic snakes in the North East are still called by Biblical names 'TSEFA' and 'EF'. The occurrences of snake bite hemorrhage in antiquity is similarly indicated by beliefs of certain primitive people associating menarche and snakebite [22].Two hundreds years ago

Fontana (1787) noted that blood remained fluid in animals killed by viper bite. Mitchell (1860) reported the same phenomenon following American Pit vipers. Lamps (1901) reported the same with Russell viper bite. Mellan (1909) showed snake venom causes defibrination. Lewis (1956) experimentally classified snake venom into fibrinolytic, thrombic, thromboplastic and fibrinogenolytic categories.

PATHOGENESIS OF SNAKE BITE HEMORRHAGE:

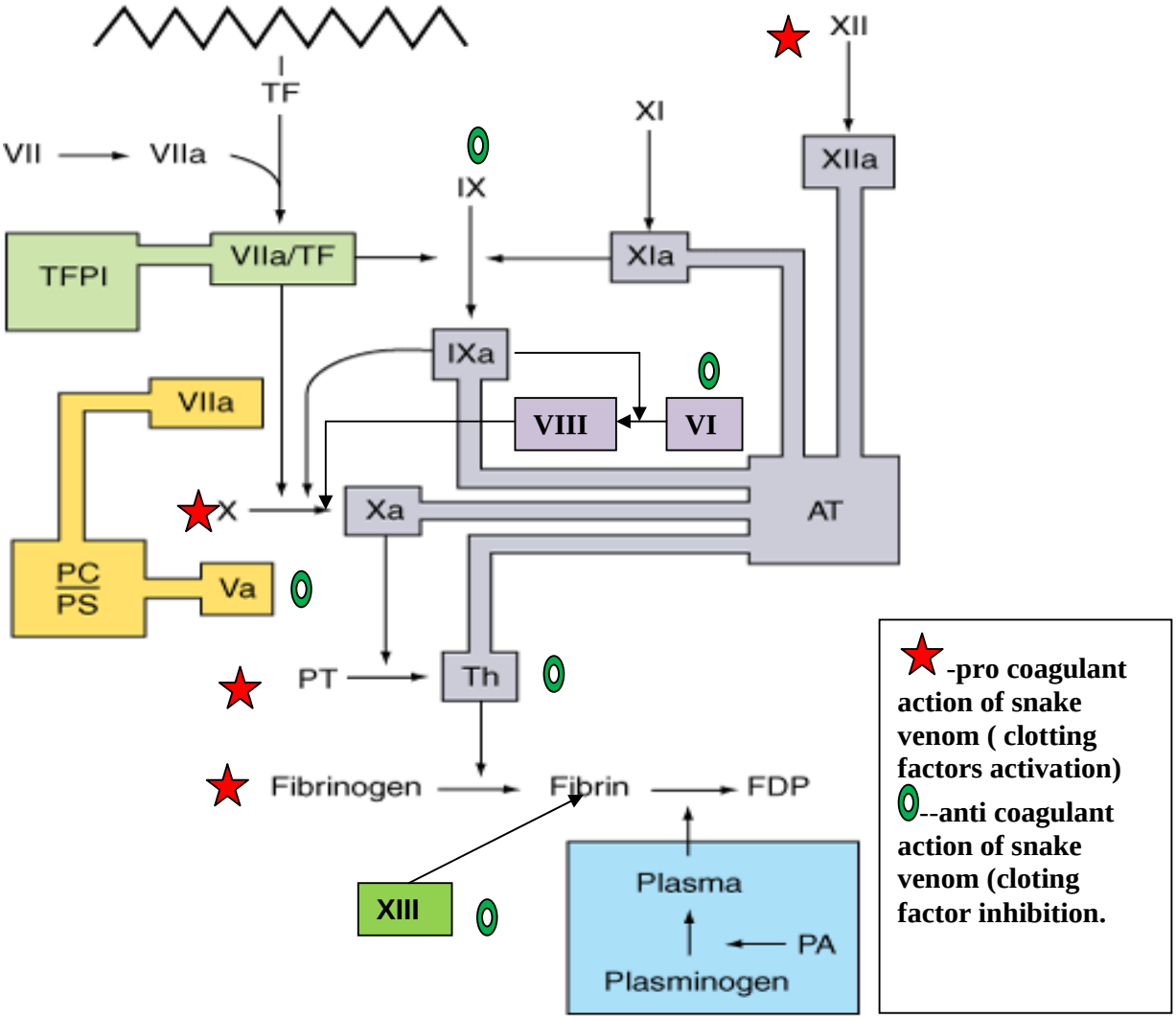
The pathogenesis of snake bite hemorrhage involves coagulation disturbances by venom anti-coagulants or coagulants, thrombocytopenia & vessel wall damage caused by venom hemorrhagins.

IN VITRO ACTION

Venoms may be broadly characterized by their effects on human or animal blood as coagulant or anti-coagulant. The distinction still holds in the literature although the assignment of a snake venom to one of these groups is often difficult in that the same venom may have both activities in vitro according to the concentration, method of collection, geographical area, season and method of storage.[22]

(ii) Coagulant activity

SNAKE VENOM AND THE COAGULATION PATHWAY



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Prothrombin-thrombin conversion.

- FACTOR X ACTIVATION:

Russells Viper, Echis colorstus, Naja Nigricollis and various snake venoms promote prothrombin to thrombin transformation. The Coagulation Biography of Russell Viper Venom published by Macfarlane 1967 used venom for clot promoting activity of hemophilic patient blood applied as local hemostatic. Mechanism of prothrombin to thrombin conversion follows factor X activation.[22]. Factor X is activated by active factor VIII. It is said that Russell Viper venom resembles factor VIII.[23].

- DIRECT PROTHROMBIN ACTIVATION:

Block demonstrated lack of participation of factor X in thrombin formation induced by Tiger snake venom.[24]. It was found to activate prothrombin directly.

- FIBRINOGEN – FIBRIN CONVERSION:

Von Klobusitzky isolated a potent coagulation fraction which he designated as " Hemocoagulase".[25]. A commercial preparation of venom coagulant "Repltilase" had similar properties. Its activity is similar

to that of thrombin. Coagulant preparation “BOTHROPASE” is obtained from Bothrops Jaramaca Venom.

(iii) ANTI COAGULANT ACTIVITY:

1. Inhibition of prothrombin – thrombin conversion and other clotting factors.

Naja naja (Cobra) venom has exclusive anti coagulant activity by inhibition of prothrombin to thrombin conversion. Other anti coagulant activity of venoms include inhibition of factor V, VIII, IX reversibly. Phospholipase components of the venom could also lead to destruction of the clotting factors.[22]

2. Fibrinogenolytic activity: Echis coloratus venom has fibrinogenolytic action at low concentration.[26,27].while naja naja nigricolis is coagulant at high concentration and fibrinogenolytic at low concentration.[26,27].
3. Fibrin stabilizing factor inactivation: Echis coloratus venom is demonstrated to inactivate fibrin stabilizing factor in plasma independently from clotting process.[22]
4. Other Mechanisms: The anti coagulant action of many venoms is still controversial. Some studies have shown

Russell Viper venom acts only indirectly and not directly. It is said to act by releasing heparin like anti coagulant factors.[22]

(iv) FIBRINOLYTIC ACTIVITY:

Most of the venoms which are fibrinolytic are also fibrinogenolytic.

(v) ACTION ON PLATELETS

Echis corolatus venom at high concentration lyses isolated platelets and liberated from them pyro phosphatase. Bothrops reptilase clotted platelets and fibrinogen. It produces loose platelet aggregates and releases platelet serotonin and adenine neucleotide.

IN VIVO ACTION

(A) Disseminated Intra Vascular Coagulation

Incoagulability of blood in animals dying from viper bite was mention in eighteenth century by Geoffroy (1737) and Fontana(1767). Its now generally accepted that the incoagulability produced by venom is primarily due to intra vascular coagulation. The mechanism of induction of intra vascular clot varies with different species. As already discussed above, it occurs mainly by the direct

conversion of fibrinogen to fibrin or prothrombin to thrombin or factor X and XII activation by the venom.[22]. Direct pathological evidence for intra vascular clotting in humans is a demonstration of intra vascular clot. But their absence on autopsy does not rule out disseminated intra vascular coagulation as fibrinolysis can occur in the postmortem period. So the demonstration of a clot depends on the time between venom injection, dose of venom and the time of autopsy.[28].

(B) Primary fibrinolysis In some cases it was found that when the blood was left to stand in a test tube for sometime it resulted in formation of a clot which then lysed after few minutes. This led on to the study of any other mechanism other than disseminated intra vascular coagulation being responsible for bleeding abnormality. A suggested mechanism was the direct fibrinogenolytic activity of venom.

The importance of knowing whether primary fibrinolysis acts in a significant manner in snakebite coagulation disturbances is of practical therapeutic importance. In case the coagulation disturbance is primarily DIC early stages would be benefited by heparin therapy (while in case of primary fibrinolysis the condition will be worsened by heparin). The points used for differentiation between primary fibrinolysis and DIC are listed in the accompanying table.

	PRIMARY FIBRINOLYSIS	DIC
INCIDENCE	Exceedingly rare	Fairly common
PLATELET COUNT	Normal	Low
FIBRIN MONOMERS (PROTAMINE TEST)	Negative	Positive
FIBRIN DEGRADATION	Very large amount	Variable amount
CLOT LYSIS	Very rapid after formation of clot	No clot formation / variable
PERIPHERAL SMEAR	Normal	Fragmented RBC

Studies in India have produced varying results. In a study conducted by Mohapatra and Nayak in 43 cases of Viper Bite Disseminated Intravascular Coagulation was the predominant coagulation abnormality.[30]

In another study by Saini, Sharma on thrity cases of viper bite, primary fibrinolysis was seen as the predominant change. Majority of studies have proved primary fibrinolysis as a less important mechanism.[31].

(c) Inactivation of Fibrin Stabilising Factor

Though in vitro inactivation of fibrin stabilizing factor following Echis coloratus has been demonstrated, in vivo inactivation is mainly a consequence of intravascular clotting.[22]

(D)Thrombocytopenia

It is known to accompany clinical and experimental defibrination. Apart from the fact that the platelets are trapped in intravascular clots venom factors (possibly phospholipase A) contribute to platelet damage. Clinically even in those cases in which

thrombocytopenia is a feature, the hemorrhage of snake bite lacks the characteristics of thrombocytopenia in that petechiae are absent[22]. It is now concluded that thrombocytopenia is not the primary cause of envenomation hemorrhage but may be a aggrevating factor.[22].

(vi) Hemorrhagins

Incoagulability without hemorrhage was observed both clinical and experimentally in a few cases.[11,12]. This led to the assumption that hemorrhage in snake bite also occurs due to mechanisms other than coagulation disturbance. This led to the discovery of vessel wall damaging factor termed hemorrhagin in the snake venom.[22]. Earlier studies by Flexner found that these toxins cause rents in the vessel wall.[32] Fulton has observed initial arteriolar constriction with sluggish circulation and subsequently red cells spurting through the vessel wall one by one without apparent damage of endothelium. It was concluded red blood cells spurt through pores developing in the region of the inter- endothelial substance.

(vii) Supression of Fibrinogen formation

Snake venom is said to inhibit fibrinogen formation in the liver but this is not well established.[11].

ALTERATION IN COAGULATION PARAMETERS IN A CASE OF SNAKE BITE

Till today the main information for us about alteration in coagulation profile is based on the study by Reid. In his study 97 patients admitted following bite of Malayan Pit viper with features of envenomation were observed. Of these 54 were treated with Anti-Snake Venom and 43 where treated symptomatically as Anti-Venom was not available. From both of the above groups 29 selected patients were studied for changes in coagulation parameters. A similar study was conducted in India by Mohapatra following viper bite in Orissa.[30]

CLOTTING TIME

In Reid's study all the cases had prolonged clotting time. The quality of the clot was also assessed by making the blood stand in a test tube undisturbed for 72hrs. they were graded as follows:-

Grade 1 – Normal – cell deposits at the bottom of test tube do not rise above the bottom curve of the tube. Clot formed was about 50% of original whole blood volume.

Grade 2 – Slight Defect – cell deposits increased above the bottom curve of the tube upto30% of original whole blood volume. Clot size diminished in proportion.

Grade 3 – Moderate defect – cell deposit is 30% to 50% of original volume. Clot size is about half the size of a contracted normal clot.

Grade 4- Severe Defect- cell deposit is 50% or more of the original volume. Clot size is A Small speck.

Grade 5- No clot.

It was found that in all cases of envenomation clot quality was abnormal from Grade -2 to Grade -5 with clot lysis maximum within 5 hrs.(Normal is by 72hrs).[11] In the Indian study clotting time was prolonged in 95% cases while clot quality was abnormal in all cases. 5% cases with normal clotting time had prolonged thrombin and prothrombin time.[30].

BLEEDING TIME AND TOURNIQUET TEST:

Ten percent cases showed prolonged bleeding time in the Orissan study while Reid's study showed only 5% prolongation. Tourniquet test was positive in 4% cases.[11,30]

THROMBIN TIME / PROTHROMBIN TIME / ACTIVATED PARTIAL THROMBOPLASTIN TIME:

Thrombin time and prothrombin time were prolonged in both the studies. Activated partial thromboplastin time done only in the orissan study also showed prolongation in all cases.[3,33].

EUGLOBULIN LYSIS TIME:

Done to diagnose primary fibrinolysis, it was positive only in 5% cases. But a study by Saini to differentiate DIC from primary fibrinolysis by Euglobulin lysis time, protamine Sulphate Test showed 90% positivity suggestive of primary fibrinolysis.[30,33].

FIBRIN DEGRADATION PRODUCT:

It was found to be elevated in all cases of envenomation.[30]

FIBRINOGEN:

It was invariably low ranging from 10 to 160 mg/100ml in all cases.[11,30]

PLATELET COUNT:

Count was 1 lakh and less in 93% cases. Reid's studies showed a platelet count reduction in 95% cases. Saini's study showed only 10% cases with reduction in platelet count.[33]

:

NATURAL COURSE OF RETURN OF COAGULATION PROFILE TO NORMAL

It was found that in those cases where anti-venom was not given despite moderate or severe systemic poisoning, coagulation defects persisted for an average 15 days (range 6 to 26 days)[11].(In the Indian study severe envenomation changes reverted back to normal in 7 days and cases of mild envenomation in 2 to 3 days.

CHANGE IN COAGULATION PROFILE FOLLOWING ANTI SNAKE VENOM ADMINISTRATION:

It was found that with specific anti-snake venom therapy correction of coagulation defect was remarkably rapid regardless of time elapsing between bite and anti-venom therapy[11].. When fixed, adequate amount of anti-snake venom was given in cases of Malayan pit viper coagulation returned to normal on average in 9hrs. (range 2 to 18 hrs). Relapse of coagulation abnormality was not found when adequate high dose was given initially. In case where low doses were used relapse of abnormal coagulation parameters after reverting to normal was noted.In 11patient following Haffkine polyvalent Anti-snake venom it took 24 – 48 hrs to revert to normal. Clot quality,

bleeding and clotting time, prothrombin fdtime, activated partial thromboplastin time reverted to normal in 57.9% cases in 24 hours, 95% cases in 48 hours. Thrombin time, fibrinogen and platelet count took 3 -4 days to revert to normal.[11,30].

CHANGES IN COAGULATION PROFILE FOLLOWING BLOOD TRANSFUSION AND FIBRINOGEN INFUSION:

Although blood transfusion improved the general condition of the patient if shocked or anaemic it did not shorten the duration of coagulation defect.[11]. With fibrinogen infusion coagulation profile temporarily reverted to normal only to return in a more severely abnormal form.

In conclusion the alteration in coagulation parameters in a patient bitten by a poisonous snake occurs by multiple mechanisms, the principal one being DIC, and the best way to correct it is with antisnake venom therapy.

MATERIAL AND METHODS

STUDY POPULATION

This study was undertaken in Thanjavur Medical College Hospital in the period between july 2007 to October 2008 . Patients selected were among those admitted to the general medical wards following snake bite.

SELECTION CRITERIA

Patient giving history of bite with definitive evidence of snake bite in the form of local cellulites, regional lymph adenitis and / or prolonged clotting time (taken as suggestive of viper bite) were considered for the study. Patients presenting with neurotoxic manifestations were not considered for the study. Patient having local swelling due to tourniquet application and local native treatment were again not considered for study.

BASIC INVESTIGATION

For all the cases routline hemoglobin, total and different count of WBC, urine deposits, blood sugar, urea and serum creatinine were estimated.

GRADING OF SEVERITY

Patients were graded as follows:

Grade I : Local cellulitis, regional lymph adenitis, normal clotting time.

Grade II: Prolonged clotting time + local features.

Grade III: Presence of systemic bleeding + prolonged clotting time[-15].

WHOLE BLOOD COAGULATION TIME

Though there are various methods of assessing the clotting time, (the normal by Lee and White – 6- 9 minutes, by Dale & Laid -3-5 minutes) the method selected for our study was that of Ulans, for practical reasons. By this method two ml of blood was kept undisturbed in a pyrex test tube (10cm tall and inside diameter 1cm). After 5 minutes test tube was gently tilted to 45 and tested for clotting. Procedure was repeated every minute until the blood clotted. The normal clotting time

by this method was in the range of 9 to 15 minutes.[35] The sample was left behind to assess the clot quality as described earlier.

BLEEDING TIME

Bleeding time was estimated by Duke's method. Here, a needle – prick was given on the tip of the finger, about one centimeter deep, and the blood blotted off. The time taken for the bleeding to stop was noted. Normal range: 3 to 5 minutes.

PLATELET COUNT

The stain used was brilliant cresyl blue prepared by mixing 0.3gms of brilliant cresyl blue crystals with one drop of formalin and 100 ml of distilled water. Using a RBC pipette blood was taken upto the 0.5 reading and brilliant cresyl blue fluid (1 in 200 dilution) till the 101 mark. It was left for two minutes and then charged with a cover slip into a neubars chamber. Platelets were seen as bluish pink spots. Normal range – 1.5 – 3 lakhs/cubic mm.

BLOOD COLLECTION AND PROCESSING FOR COAGULATION PROFILE TEST

Blood withdrawn from a vein was mixed with 3.8% aqueous trisodium citrate in the ratio of 9 volumes of blood to 1 volume of citrate solution. (i.e., 1.8 ml of blood with 0.2 ml of sodium citrate). Blood was taken immediately to the laboratory. In case of delay, samples obtained were stored in a freezer at 4 degree Celsius. In the laboratory, centrifugation at 3000 rpm was done for 5 minutes. Resultant sample was used for the following tests. Control blood samples were also taken and similarly processed.[36]

Samples were taken before administration of Anti snake venom. In a few selected cases samples were taken after anti snake venom administration.

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PROTHROMBIN TIME

Although originally thought to measure prothrombin the test is now known to depend also on reactions with factors V, VII

and X and fibrinogen concentration. Thus the name prothrombin time is not accurate. This test measures the effectiveness of extrinsic pathway. Test was done with both patient and then control plasma. 0.1 ml of plasma in glass tube was placed in a water bath at 37c for 3 – 5 minutes and 0.2 ml of Liquiplastin reagent (Thromboplastin) was added. Time taken for the sample to clot was noted. Normal values depend on the thromboplastin used. The normal is 10 – 14 seconds over the control value [36] .

ACTIVATED PARTIAL THROMBOPLASTIN TIME

This tests abnormalities of all coagulation factors except factors VII and XIII. It is especially sensitive for early stage of intrinsic pathway. With 0.1ml of test plasma 0.1ml of Liquicelin reagent solution was mixed for 3 minutes at 37c in water bath. 0.1 ml of prewarmed calcium chloride was added and stop watch started end pointed recorded. Abnormal values should exceed control value by 6 seconds. More than 10 seconds is definitely abnormal.[36]

THROMBIN TIME

0.2ml of sample plasma was incubated at 37c for 2 minutes. 0.1ml of thrombin time reagent was added and stop watch

started. Clotting time was measured. Test is repeated in two test tubes with patients plasma and control plasma. 20 seconds and over are abnormal. Patients value should be within two seconds of control value.[36]

FIBRIN DEGRADATION PRODUCT

The reagent used in this test was Dimertest II latex reagents coated with mouse monoclonal Anti-D dimmer antibody. Serial dilutions of the test plasma were prepared. For 1:2 dilution, 100 microlitres of plasma were added to 100 microlitres of phosphate buffer solution. For 1:4 dilution 100 microlitres of 1:2 dilution solution were added to 100 microlitres of 1:2 dilution solution were added to 100 microlitres of phosphate buffer solution. This procedure was repeated to extend to the desired dilution. For each of the dilute solutions 20 microlitres of plasma were added and mixed with reagent solutions. Slide was rotated gently for 3 minutes. At the end of 3 minutes agglutination is checked for .

Highest dilution in which visible agglutination occurs is taken as a titre.

INTERPRETATION OF RESULTS

TITRE	APPROXIMATE XL-FDP LEVELS (mg/1)	UNDILUTED	SAMPLE DILUTION		
			1:2	1:4	1:8
0	Normal	-	-	-	-
1	0.25 – 0.5	+	-	-	-
2	0.5 – 1	+	+	-	-
4	1 – 2	+	+	+	-
8	2 – 4	+	+	+	+

Plasma from normal individuals is not expected to agglutinate.

FIBRINOGEN

Reagents used: 1) Ammonium sulphate -13.3gms of ammonium and 1gm of sodium chloride in 100ml of distilled water. ph is adjusted by adding 10N NaOH.

2) Normal saline – 9mg of sodium chloride in 1 litre of water.

TEST	**BLANK**
0.5 ml plasma and 0.5ml Normal saline added to 9ml of ammonium sulphate solution	1ml of normal saline added to 9ml of Ammonium sulphate

Shake and read after 5 minutes with 420 filter.

Result = test – blank = Blood fibrinogen in milligram%

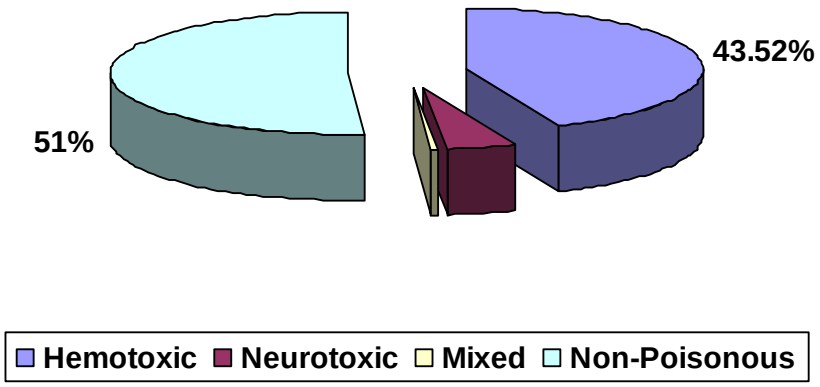
(Normal 200 – 400mgm%)

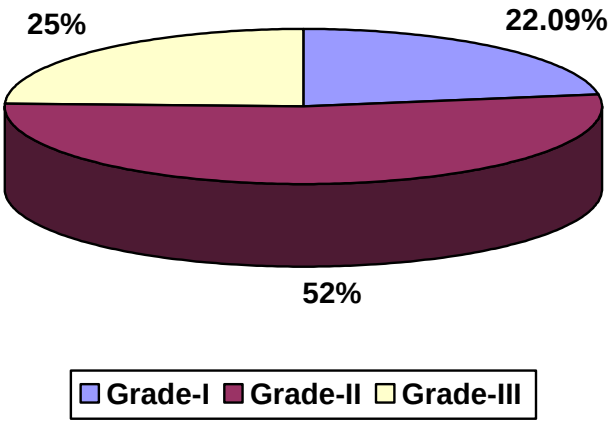
ANALYSIS OF RESULTS

GENERAL FEATURES

A total of 147 patients were admitted in Thanjavur medical college hospital general medical wards from july 2007 to October 2008 with either history or features suggestive of snake bite. Of the 147 patients 64 had features suggestive of hemostastic abnormality. Seven patients presented primarily with neurotoxic manifestation. One patient had hemostatic and neurotoxic abnormality. Rest of the 75 patients had no features of envenomation. Another 117 patients were treated as unknown reptilian bite. Thus of 147 patients admitted with either history or clinical features suggestive of snake bite 48.9% were poisonous and 51.1% were nonpoisonous. Of the poisonous bite 89% had primary coagulation abnormality and 9.7% had neurotoxic manifestion and 1.3% both.

Of the 64 patients admitted with features for primary haemostatic disturbance fourty eight were selected at random for the study. The average age of the patients in our study was 38 yrs ranging from 7 yrs to 65 yrs.


43.52%
51%
Hemotoxic
Neurotoxic
Mixed
Non-Poisonous


25%
22.09%
52%
Grade-I
Grade-II
Grade-III

The study population was separated into 3 categories Grades I, II and III according to clinical features and clotting time. Eleven patients belonged to grade I, 25 to Grade II, and another 12 to Grade III (22%, 54%, 24%) respectively. These patients were subjected to various coagulation parameter assessment tests. Majority of the patients had bite on the lower limb – 63.6%. The incidence of bite in the upper limb was 36.4%. The average duration of hospital stay of the snake bitten individuals with clotting abnormality was 6 days, ranging from 3 to 31 days.

ASSESSMENT OF CHANGES IN COAGULATION PROFILE:

Blood for assessment of changes in coagulation were taken at the time of admission before therapy was started in patients who had definite features of envenomation, excluding neurotoxic manifestations.

1. **Clotting Time:**

Of the forty eight patients selected for study, 76% has prolonged clotting time at the time of admission. In another 3 cases (6.2%) clotting time was normal at the time of

admission, but turned abnormal in a period of 4-12hrs. Thus in total 82% of the patients had prolonged clotting time.

2. Bleeding Time:

Bleeding time was analysed in forty out of the total of 48 cases. In all cases it was found to be normal, even in those cases who had systemic bleeding manifestatious in the form of haematuria, haematemesis and haemoptysis. The average bleeding time was found to be 2 – 6 minutes

3. Platelet Count:

Platelet count was found to be reduced in all cases belonging to both Grades II and III. The average platelet count was 97,486 cells/ cumm. Thus a 100% reduction was noted. The average count in Grade I was 2.3 Lakhs.

4. Prothrombin Time:

This test is done primarily to evaluate any abnormalilty in extrinsic pathway. It was done in ten out of eleven cases belonging to grade I [that is local features with normal clotting time]. The test was found to be normal in all but one patient. This patient who belonged to grade I with prolonged prothrombin time went on to develop abnormal coagulation profile over a period of six hours. Another two patients who ;had similar clinical condition showed a normal prothrombin time.

In Grade II 21 out of 25 cases were evaluated for prothrombin time and in Grade III 10 out of 12 cases were tested. All these patients showed prolongation of prothrombin time denoting a 100% positivity.

PT level assessed in patients following anti snake venom therapy showed a normalization by forty eight hours.

5. Activated Partial Thromboplastin Time:

APTT test is done to evaluate any abnormality in intrinsic pathway. Test was done in 10 out of 11 cases in Grade I were normal except for 1 patient who latter went on to develop abnormal coagulation features. The test done in 20 patients of Grade II and 10 of Grade III were prolonged. Thus the test was 100% positive in patients belonging to Grades II and III. APTT was found to be prolonged up to a period of 48 hrs following ASV therapy

6. Thrombin time:

This test was done in eight cases with Grade I envenomation. It was normal in all of them including those cases where PT and APTT were prolonged and patients later went on to develop abnormal coagulation. In grade II and III categories, tests were done in 20 out of 25 and 10 out of 12 cases respectively. They showed 100% prolongation as in case of PT and APTT. The test returned to normal by 48 hrs.

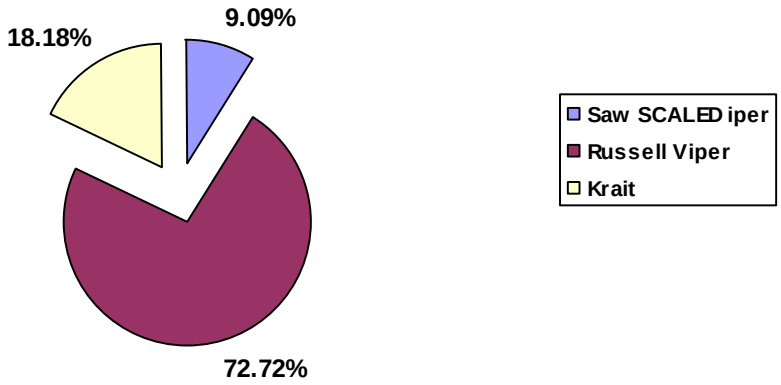
7. **Fibrin degradation products**:

This test detects fibrinolysis occurring as a primary or secondary phenomenon. This was done for 6 cases belonging to grade. I. All if them showed no evidence of fibrinolysis. In 16 cases belonging to grade II 64.9% showed positive results in a dilution of 0.5mg and 35.1% in a dilution of 1 to 2. Thus the test was 100% positive. In grade III patients, test done in 5 out 12 cases, eighty percent showed positivity in dilution 0.5 to 1 and the next 20% in 1 to 2mg. hence the test was again 100% positive.

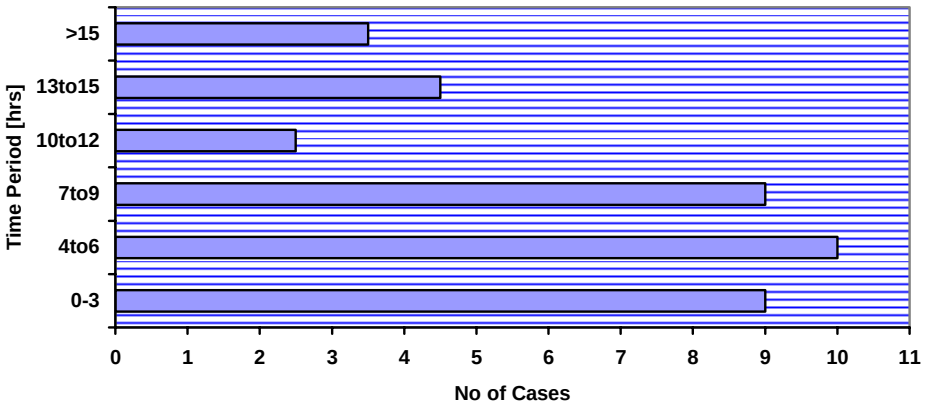
8. Fibrinogen:

Plasma fibrinogen was estimated in all patients. Patients belonging to Grade I showed an average level of 245.5mgs [Normal 200 to 400 mg / dl].fibrinogen levels studied in grade II category showed an average of 166.7mgs and in grade III 143.9mgs. Thus there was 100% reduction in fibrinogen levels in Grade II and III categories.

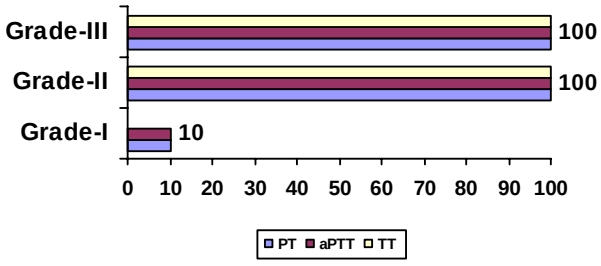
Species of Snakes Causing Coagulation Abnormality



Onset of Coagulation Abnormally



Analysis Prothrombin&Activated Partial Thrombo plastin Time&Thrombin Time



CORRELATION OF COAGULATION ABNORMALITY WITH THE TYPE OF SNAKE:

In 11 out of 48 patients [23%] the snake was killed and brought to the hospital and thus could be identified. The 77% sustained an unknown bite which was later treated as snake bite based on clinical evaluation. Among the patients who identified the snake 72% was saw scaled viper bite. 18.3% identified the snake as Russell viper and one patient who expired had sustained a Krait bite.

ANALYSIS OF SYSTEMIC BLEEDING MANIFESTATIONS IN SNAKE BITTEN INDIVIDALS:

A total 12 patients out of 48 had systemic bleeding. Out of them 33.33% presented with haematuria while 58.3% had gum bleeding and 25% of individuals had haemoptysis and 8.3% hemetemesis and 8.3% epistaxis.

ANALYSIS OF THE TIME INTERVAL BETWEEN SNAKE BITE AND ONSET OF COAGULATION ABNORMALITY:

The time of onset of abnormal coagulation was analysed based on two sets of findings. The first was based on the number of patients who had prolonged clotting time at the time of admission. 77% of patients had abnormal clotting time at the time of admission. The average time period between the bite and hospital admission was 7.15 hours ranging from 2 hours to 12 hours.

The second group analysed has a set of three patients who had normal clotting time at the time of admission which become abnormal over a period of time. Two of them developed it in a period of 6 hours and the third patient by 12 hours. Thus it was concluded, that the onset of abnormal coagulation occurred as early as 2 hours and late as twelve hours with a majority developing it in an average time of seven hours.

All patients who had prolonged clotting time at admission also had a prolonged PT, TT, and FDP. One patient who had initial normal clotting time and went on to develop abnormal coagulation had prolonged PT and APTT at the initial instance itself.

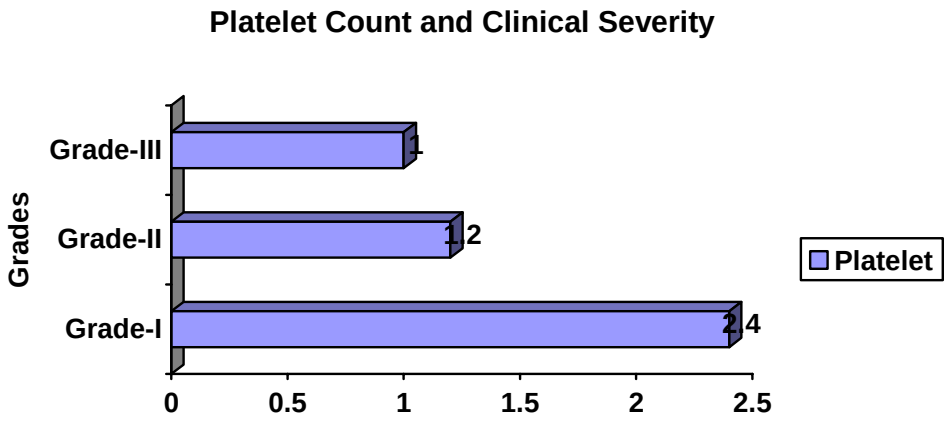
CORRELATION OF CLINICAL SEVERITY WITH QUANTITATIVE COAGULATION TESTS:

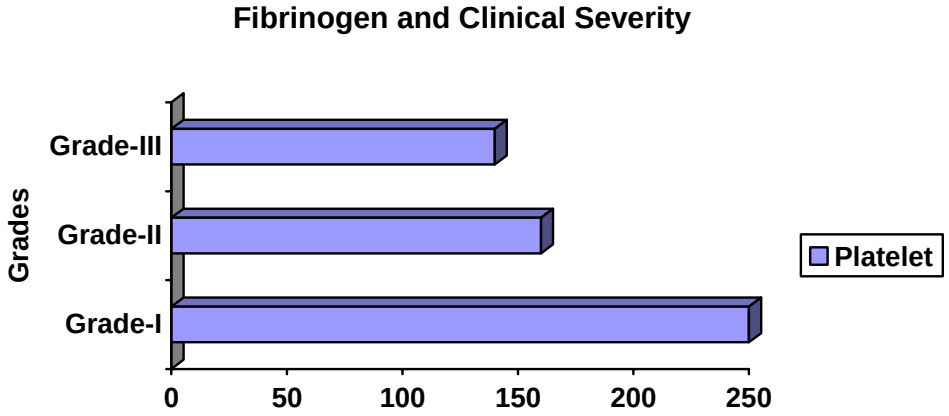
Three quantitative tests namely FDP, platelet count and fibrinogen were analysed in relation to clinical severity.

FDP was negative in all patients belonging to grade I. In grade II patients, the test was positive in a dilution of 0.5 to 1 in 64.9% cases and 1 to 2 in 35.1%. In grade III, 80% showed a positive result in a dilution of 0.5 to 1 and 20% in a dilution of 1 to 2. Thus in conclusion FDP level did not correlate with the clinical severity assessment.

Platelet count was normal in all patients belonging to Grade I with an average of 2.3 lakh/cumm. The average platelet count in grade II individuals was 1.01 lakh/cumm and grade III 90,400/cumm. Thus, though the platelet count was reduced in all snake bitten individuals with coagulation abnormality, it did not
correlate with severity of envenomation.

Blood fibrinogen analysis done in patients of grade I showed no reduction, the average level was 245mg/dl. Grade II patients had an average level of 166mg/dl and grade III 143 mg/dl. Thus the level of serum fibrinogen was found to be decreasing with severity of envenomation.


Platelet Count and Clinical Severity
Grades
Grade-III
Grade-II
Grade-I
1
1.2
2.4
0
0.5
1
1.5
2
2.5
Platelet


Fibrinogen and Clinical Severity
Grades
Grade-III
Grade-II
Grade-I
0
50
100
150
200
250
Platelet

ANALYSIS OF THE TIME TAKEN FOR THE RETURN OF COAGULATION PROFILE TO NORMAL:

The time taken for clotting time to turn normal was analysed in grades II and III. For proper standardization of fixed regimen of ASV was used. Clotting time was repeated every second hourly and in certain cases at more frequent intervals. In grade II the average time taken for the clotting time to turn normal was 7.9 hours. The range was from 2 to 21 hours. In grade III individuals the average time taken for clotting time normalization was 18 hours, the range being 4 to 24 hours. The average dose of ASV needed in grade II individuals was 13.8 vials (5 to 40), in grade III 15.5 (10 to 30 vials).

The time taken for the return of PT, APTT, TT, FDP, fibrinogen and platelet count to normal following ASV therapy was studied in four patients who had normal clotting time at admission though it was initially prolonged when managed in peripheral hospitals. PT, APTT and TT, fibrinogen FDP and platelet counts were abnormal in two patients in whom the test was done at forty eight hours. In two other patients in whom the test was done on 3rd and 5th day, only FDP fibrinogen and platelet were abnormal. PT, APTT and TT had normalized. Thus the average time taken for normalization of PT, APTT, TT was found to be 48 hours and while that taken for platelet count FDP and fibrinogen to return to normal was longer

ANALYSIS OF RELATIONSHOP BETWEEN THE TIME OF BITE, INITIATION OF THERAPY, RETURN OF COAGULATION PARAMETERS TO NORMAL AND THE DEVELOPMENT OF COMPLICATIONS.

TIME TO ONSET OF TREATMENT (HOURS)	GRADE	NUMBER OF CASES	NUMBER OF CASE RENAL FAILURE	RETURN OF CLOTTING TIME TO NORMAL	AVERAGE NO OF ASV
0-5	G II	10	-	8.8	14.5
	GIII	3	-	9	15
5-10	G II	8	2	8.7	14.5
	G III	5	1	11.6	17
10-15	G II	4	2*	10	10.5
	G III	2	1	11	11.5
> 15	G II	3	1*	7	8
	G III	2	1	20	15

** (PATIENTS ADMITTED WITH ESTABLISHED RENAL FAILURE TREATED OUTSIDE TMCH)

It is evident from analysis of the above table, that the time of onset of therapy correlate with the development of complications in hospital-

treated individuals. The incidence of renal failure has been found to be high if treated late.

The return of clotting time to normal following therapy with ASV correlate with the time period between bite and onset of treat ment and also by the severity of envenomation.

ANALYSIS OF INCIDENCE OF RENAL FAILURE IN RELATION TO ALTERATION IN COAGULATION PROFILE:

In total 19% of the study population developed renal failure of which 11% belonged to grade I, 55.5% to grade II and 33.3% to grade III. Patients in grade I who developed renal failure had a normal coagulation profile.

55% of the renal failure was from grade II, but the important observation was 3 out of the 5 patients who developed renal failure in this group had developed the disease before hospitalization in thanjavur Medical College Hospital. They had been managed with low dose ASV (an average of 5 vials) in the peripheral centre. Only two of the twenty two patients belonging to grade II developed renal failure during hospital therapy. Thus excluding those patients who had established renal failure at the time of admission, only 9% of hospital treated individuals

developed renal failure in Grade II. The average FDP level was 0.5 to 1 mg/dl in these patients. The average platelet count was 1.2lakhs / cumm and fibrinogen level was 185mg / dl.

In grade III, 3 out of 12 patients (25%) developed renal failure despite hospital treatment. The FDP level in two patients was 0.5 to 1 and one of them was 1 to 2 mg/dl. The average platelet count was 85,000/cumm and fibrinogen level was 124 mg/dl.

Three patients in grade II were treated by peritoneal dialysis (one sitting) while one patient was managed conservatively. In grade III two patients were managed conservatively while one needed two sittings of peritoneal dialysis.

Thus in conclusion, the severity of envenomation correlated with the development of renal failure in hospital treatment individuals. As in case of severity, fibrinogen levelcorrelated well with development of renal failure than platelet count and FDP

DISCUSSION

EPIDEMIOLOGICAL ASPECT

The cauvery basin, comprising the areas in and around thanjavur, is a highly fertile area. The primary occupation of the people in this area, for several generations has been agriculture.

This abundance of farmland, which is the natural habitat of snakes such as the viper has meant that there has been a constant high incidence of snake bite cases over the past several years presenting to our institution. Of these, the commonest presentation has been with hemostatic abnormalities and this has prompted us to conduct a study on the coagulation failure following snake bite. In an hospital analysis of the statistics for the period 2005 to 2007 revealed that the maximum number of cases were admitted during the monsoon period. Hence this study was conducted during this period.

The incidence of snake bite and its severity is well known to increase during the rainy season. In North India, 80% of bites per annum occur between May and October, while in North Kerala it occurs between October to January. [16,17]

A total of 147 cases were admitted following snake bite in this period. Of these, 48.9% had features of envenomation. 89% was hemotoxic, 9.7% was neurotoxic and 1.3% was of the mixed variety. It is known in India, out of 236 species of snakes, only 50 are poisonous. Commonly encountered snakes include krait, cobra, saw-scaled viper and Russell viper.[2] Taking these into consideration, the incidence of envenomation has to be low compared to the total number of bites. Our study shows 48.9% of snake bite victims had envenomation features. This high incidence may be due to the fact that a large number of non-poisonous snake bite may have been treated at local hospital or, if referred here, may have been recorded under the separate category of unknown reptilian bite.

As we have mentioned already, the greater incidence of patients presenting with hemostatic abnormality (89%) compared to neurotoxic group (9.7%) may be related to the natural habitat of snakes, viper being the principal offender (farmland habitat).

Percentage of patients with bites in the lower

limb in our study was 63.3% and upper limb 36.7%. This correlated with other studies as shown by Sawai in 1974(lower limb bite – 72% ; upper limb bites -25% , 3% other part s).

The average duration of hospital stay in our study was 6 days (range – 3 to 31 days). The reason for prolonged hospitalization included the development of complication like renal failure and gangrene secondary to compartmental syndrome.

CHANGES OBSERVED IN COAGULATION PROFILE.

Clotting time

The study conducted by Reid reported 100% prolongation of clotting time in all cases of definite envenomation.[11] In Orisa study 95% had a prolonged clotting time.[30] 6% of these developed abnormality after admission, 6 to 12 hours later. This emphasis the fact that local cellulitis and lymphadenitis is an important clue for viper bite. Cases that had local features but normal clotting time, also may have to be treated with ASV as they may later develop coagulation abnormality – as in 6% of our cases – or, may develop other complications such as acute renal failure (one case in our study). 3 patients had no local

features but had prolongation alone cannot be taken as a 100% reliable indicator of hemotoxic envenomation. When clotting time was considered with local features, the specificity was significantly increased (especially viper bite)

Bleeding time

Only 10% showed prolonged bleeding time in the study conducted in Orissa.[30] The incidence reported by Reid was 5%

In our study, none of the patients including those with systemic bleed, had an abnormal bleeding time. We infer that though platelet abnormality may be a contributory factor, it is not the major cause of bleeding.

Platelet count

Studies by both Reid and Mohapathra (in Orissa) showed a reduction in platelet count in 95% and 93% respectively. [11,30]. Saini et al reported a 10% incidence of reduced platelet counts.[33] We observed a reduced platelet count in all cases (average count – 97,486/cu. Mm.) with prolonged clotting time. However

there was no significant correalation with severity. Even patients having mucosal bleeds (hematuria, hemetemesis) had only moderately reduced platelet counts (not sufficient to cause spontaneous bleeding) and normal bleeding times. Hence, we conclude that the effect of direct vasotoxic toxin – " hemorrhagin" – must be a significant factor in causing mucosal bleeding.[22]

Prothrombin, activated partial thromboplastin & thrombin times.

Thrombin time, prothrombin time and activated partial thromoboplastin time were prolonged in all cases in the orissan study.[30] PT and TT were prolonged in all cases in Reid's study. The test was found to be prolonged even in the 5% of cases where clotting time was normal. In our study the test was prolonged in all cases belonging to grades II and III envenomation (i.e., those with prolonged clotting times) in patients with normal clotting time, the test was prolonged in only one of the eleven (9%). The significant finding was that this case was one among the three that went on to develop prolongation of the clotting time latter. In conclusion, as with other studies, PT, APTT and TT have shown prolongation in all cases with prolonged clotting time, indicating that the venom activates both intrinsic and extrinsic pathways equally. In patients with normal clotting times, the test was prolonged in all cases in the orissan study[30] but in our case only one of the patients

belonging to this category showed similar results, and this patient went on to develop clotting abnormalities later. It has been stated that while the clotting time may be normal even when clotting factors in the blood are at 1% of normal amount, PT and APTT are prolonged below a value of 6% of normal itself [37.] This suggests that the latter tests detect hemotoxicity earlier: however, further large scale studies, with more number of patients are needed to establish this. The average time taken for the normalization of these tests in our study was found to be 48 hours.

Fibrin degradation products (FDP)

FDP was increased in all cases with prolonged clotting time but not in the group with normal clotting times, even in the presense of other features of envenomation. The orissan study showed that all the patients had increased FDP.[30] We found no correlation between the severity of envenomation and FDP levels. Thus fibrinolysis (either primary or secondary) is the mechanism responsible for prolongation of clotting time and the resultant complications in viper bites.

Fibrinogen

Blood fibrinogen was reduced in all patients belonging to Grades II & III (average values 166.7 mg% and 143.9 mg% respectively). The reduction was proportionate to the severity. The other studies reported reduced fibrinogen in all cases with prolonged clotting time [11,30]

In this study, we have attempted to find out which of disseminated intravascular coagulation or primary fibrinolysis was the underlying mechanism responsible for the coagulation abnormality.

Several international studies, including the one by Reid, and an Indian study by Mohapathra et al pinpointed DIC as the primary mechanism.[11,30.] However, a study by Saini et al involving 30 cases of snake bite, reported fibrinolysis as the primary mechanism[33.] . Primary fibrinolysis, a relatively rare condition, if diagnosed by the presence of a combination of a normal platelet count, early lysis of formed clots, marked elevation of FDP and negative tests for fibrin monomers (as tested by the protamine sulphate test). However these findings were absent in our patients and hence we favour DIC as the primary mechanism.

To summarise the changes in coagulation profile, it is found that snake venom activates both intrinsic and extrinsic pathways equally, with DIC as the main factor responsible for bleeding. This seems to suggest a role for the usage of heparin in the early phase of therapy. Platelet abnormalities may be a contributory mechanism, but are not primarily responsible. Spontaneous mucosal bleeds observed may be due to directly vasotoxic hemorrhagin.

Common snake bites presenting as bleeding diathesis

Only 23% of our patients could identify the snakes of which 72.72% were saw-scaled viper bites, 18.18% Russell viper, and 9% krait. Similar distributions have been reported by other workers.[11] The majority of victims (77%) could not identify the snake they were bitten by, and hence, as suggested by Reid, we would like to emphasise that the treatment should be based more on the clinical presentation than on the identification of the snake.

Common forms of systemic bleeding

In this study 33.3% of patients with systemic bleeding had hematuria, 58.3% Gum bleeding and the rest had hemoptysis or

haemetemesis. Other common forms cited in literature are hemoptysis (Reid), and hematuria (virmani et al from Kashmir).[11]

Onset of coagulation abnormality

Practically, it is quite difficult to predict the exact time of onset of coagulation abnormality in a given case. As discussed earlier, the PT and APTT may be prolonged even before over prolongation of the clotting time.

We used those patients who developed clotting abnormalities after admission to calculate the shortest (2hours) and the longest (12 hours) intervals between bite and onset of clotting abnormality.

The average interval, calculated by including the data from patients with bleeding diathesis at admission, was 7.15 hours.

Quantitative tests in relation to clinical severity

The fibrinogen level showed some correlation with clinical severity, with the level being 166 mg% in Grade II and 143 mg%

in Grade III patients. As in other studies, none of the other tests showed any correlation, including FDP estimation and platelet counts.

Time taken for normalization of clotting time

Reid reported that the clotting time returned to normal in 9 hours with specific antiserum, and 24 hours with polyvalent serum. In our study fixed adequate doses of polyvalent serum alone were used and we found the average time for normalization to be 7.9 hours in Grade II and 18hours in Grade III envenomation. The time taken for TT,APTT and PT to return to normal was 48 hours, similar to the findings in the Orissan study. For FDP fibrinogen and platelet counts to return to normal, it took 3 to 4 days approximately.

Relationship between time of starting treatment development of complications, and normalization of clotting time

It was Reid who originally proved that the coagulation profile returned to normal rapidly with therapy, regardless of the time elapsed before the start of treatment[11.] The results of our study suggest that both the probability of complications and the time taken to achieve normalization of coagulation both depended on the severity of the bite, and the time elapsed before starting of treatment. On this

basis, and in accordance with an article published in the Lancet in 1968 [18.] concluded that ASV can be effective even if given late, and hence that there is no time limit for starting ASV therapy.

Renal failure and its relationship to clotting abnormalities

Our study showed the incidence of renal failure is 19%. In which grade II and grade III showed more incidence. The distribution according to grades showed an increasing incidence in the more severe grades from I to III . This points to a direct role for coagulation abnormality in the pathogenesis of renal failure. 3 Cases were admitted in established renal failure, after receiving treatment outside. One patient belonging to Grade I also developed renal failure, suggesting a direct effect of snake venom on the kidneys was operational in this case. Among the quantitative tests, only fibrinogen depletion and low platelet counts correlated with the development of renal failure.

C O N C L U S I O N S

1. Hemotoxic envenomation was the commonest form of snake bite poisoning seen in this study.
2. Most of the bites involved the lower limbs
3. Saw – Scaled viper was the commonest snake causing coagulation abnormality while Krait was the most poisonous (in terms of mortality)
4. Gum bleeding was the commonest form of systemic bleed observed
5. In the diagnosis of hemotoxic envenomation, the presence of local signs plus a prolonged clotting time had a sensitivity of 100%
6. Disseminated intravascular coagulation appeared to be the primary mechanism responsible for coagulation abnormality
7. Mucosal bleeding was most probably due to the direct vasotoxic action of hemorrhagin since reduction of platelet count in most cases was only moderate and bleeding times were uniformly normal
8. Snake venom acts on both intrinsic and extrinsic pathways of coagulation as all cases showed prolongation of both prothrombin and activated partial thromboplastin times.

9. Fibrinolysis is an important component of coagulation abnormality in snake bite as evidenced by reduced fibrinogen and presence of fibrin degradation products.
10. Onset of coagulation abnormality occurred as early as two hour and as late as twelve hours following snake bite
11. Prothrombin and Activated partial thromboplastin time appears to be prolonged earlier than clotting time – this needs further confirmation
12. Among the quantitative coagulation tests only fibrinogen level correlated with the severity of envenomation compared to fibrin degradation products and platelet count.

13. The time interval between the bite and initiation of treatment was found to be related to time taken for normalization of the coagulation abnormality or to the development of complications in this study.
14. Following ASV therapy, the time taken for normalization of clotting time was found to be around 8 hours in Grade II and 18 hours in Grade III individuals.
15. Direct effect of venom on the kidney was also found to play a role a longwith disseminated intravascular coagulation in the causation of renal failure.

S U M M ARY

Hemotoxic envenomation following saw –scaled viper bite was the commonest presentation in this study. The temporal pattern of coagulation abnormalities and their response to treatment were analysed. The severity of the bite was the most important factor in decicing the outcome, and disseminated intravascular coagulation was responsible for the majority of coagulation abnormalities. The findings suggest that early, adequate doses of ASV and anticipation of the complications of disseminated intravascular coagulation are the most significant aspects of management. Monitoring the coagulation status with the help of the test quoted in this study may increase our ability to diagnose coagulation abnormalities at an earlier stage, and thus may improve the management of snake bitten patients.

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PROFORMA

NAME: **AGE:** **SEX:** **IP NO:**

UNIT : **DOA:** **TIME:** **DOD :**

DETAILS OF BITE:

DATE: **TIME:** **SITE:**

FIRST AID: **Tourniquet -- Yes / No.**

Incision -- Yes / No.

SNAKE: **SPECIES:** **CONFORMED—YES/ NO.**

FEATURES OF ENVENOMATION:

LOCAL : **Fang marks -- Yes / No.**

Cellulitis -- Yes / No.

Regional -- Yes / No.

Lymphadinitis -- Yes / No.

SYSTEMIC: **Hematuria / Hemetemesis / Hemoptysis**

Epistaxis / Gum bleeding / Others.

Neurological – Ptosis/ Ophthalmology.

Dysphagia / Dysphonia.

OTHER SYSTEMS: **Pulse:** **BP:** **Resp.Rate:**

GRADE OF SEVERITY: I / II / III.

RENAL FAILURE: YES / NO.

PERITONEAL / HEMODIALYSIS: **NO. OF SITTINGS:**

COAGULATION PROFILE:

TEST	DATE / TIME:
Clotting time:	
Bleeding time:	
Platelet count:	
Prothrombin:	
APTT:	
Fibrin Degradation Products :	
Thrombin time plasma fibrinogen:	

OTHER INVESTIGATION:

TEST	DATE / TIME:
Hemoglobin:	
PCV:	
Urine deposits:	
Urea:	
Creatinine:	
S. Cholestrol:	

HOSPITAL COURSE:

DATE / TIME:	ASV:	C T:	OTHERS:

TIME TO NORMALISATION OF CLOTTING TIME:

RECURRENCE OF COAGULOPATHY : YES / NO.

MASTER CHART

s	Name	X	Ag	Ip	B	Si	Gd	Assf	Sy	Ct	Bt	Plt	Pt	Ap	Fdp	Tt	Fib	Ud	Ab	Aa	F	P	Bni	Nt
1	Krishnamoorthi	M	37	1005674	U	LF	G2	-	-	ID	3.4	110000	22	40	0.5-1	35	109	No rbc	30	0	-	-	4.5	21
2	Sumithra	F	24	1009224	U	LF	G2-1	-	-	10’	2.1	210000	14	38	0.5-1	34	190	No rbc	0	0		-	5.0	12
3	Samikanna	M	57	1005708	U	LF	G2	-	-	ID	4.1	90000	25	40	0.5-1	25	150	No rbc	20	2	-	-	14	15
4	Muthukumar	M	40	1005694	S	RF	G3	SHK	EP	ID	5.3	11000	20	30	-	37	160	No rbc	15	0	+	-	3.5	7
5	Anjali	F	50	1004254	U	LF	G1	-	-	7’	5.4	198000	14	38	0	18	220	No rbc	20	0	-	-	1	
6	Muniandi	M	35	1005685	U	RA	G3	SHK	GB	ID	4.2	88000	18	38	-	32	168	Rbc+	20	0	+	-	7.5	6
7	Balamurugan	M	18	1005643	U	LF	G2	-	-	ID	3.1	94000	18	32	.5-1	32	122	No rbc	30	10	+	-	14	7
8	Jayaperumal	M	35	1008922	S	RF	G2	-	-	ID	4.1	80000	21	38	1-2	40	-	No rbc	10	0	-	-	18	4.5
9	Thangavel	M	65	1010580	U	RF	G2	-	-	ID	2.1	85000	25	30	-	36	165	No rbc	10	0	-	-	13	6.5
10	Anthoni samy	M	52	1010598	R	LF	G2	-	-	ID	3.1	93000	-	-	-	-	240	No rbc	20	3	-	-	2	5
11	Mahendran	M	20	1008882	S	LA	G3	-	GB	ID	1.5	110000	24	32	.5-1	34	188	Rbc+	15	3	-	-	4	8
12	Agoran	M	45	1010556	U	RF	G2	-	-	ID	1.2	100000	22	30	-	28	201	No rbc	40	10	-	-	7	14
13	Rajendran	M	45	1010928	U	LF	G3	-	HP	ID	3.4	100000	16	36	-	30	109	No rbc	20	0	-	-	17	24
14	Dharmajan	M	50	1012639	S	LF	G3	-	GB	ID	0	120000	22	40	.5-1	40	-	rbc	20	0	-	-	7	24
15	Venkatesh	M	48	1012960	U	RF	G2	-	-	ID	0	96000	30	35	1-2	30	180	No rbc	10	0	-	-	5.5	8

16	Rajendran	M	30	1013022	U	RF	G2	-	-	ID	3.4	90000	20	40	1-2	30	175	No rbc	10	0	+	-	3	4
17	Janaki	F	35	1004298	U	RF	G1	-	-	12’	0	292000	14	18	0	18	275	No rbc	2	0	-	-	2.5	-
18	Duraisamy	M	45	1012949	U	RF	G2	-	-	ID	4.4	98000	18	30	.5-1	40	267	No rbc	30	0	+	-	1	7
19	Savithri	F	28	1013311	S	LF	G2	-	-	ID	2.1	96000	20	30	.5-1	40	-	No rbc	10	0	-	-	48	6
20	Mohan	M	43	1005430	U	RF	G1	-	-	6’	0	240000	14	20	0	17	240	No rbc	10	0	-	-	1.5	-
21	Veramathy	M	65	1013464	U	RA	G2	-	-	ID	1.5	110000	24	30	-	30	150	No rbc	10	0	+	-	12	8
22	Rajkumar	M	33	1005391	U	RA	G1	-	-	11’	2.3	210000	14	18	-	-	220	No rbc	5	0	-	-	2	-s
23	Dhangarthy	M	40	1013482	U	RF	G2	-	-	ID	4.1	90000	-	-	-	-	170	No rbc	15	0	-	-	8	12
24	Rajkumar	M	33	1005391	U	LA	G1	-	-	8’	2.2	-	-	-	-	-	-	No rbc	5	0	-	-	3	-
25	Karuppayya	M	43	1005438	S	RF	G2	-	-	8’	3.2	90000	18	26	1-2	22	160	No rbc	0	0	+	1	4	-
26	Kannan	M	23	1005447	U	RA	G1	-	-	5’	4.1	260000	14	18	-	18	240	No rbc	5	0	-	-	3	-
27	Rajendran	M	36	1005467	U	RA	G1	-	-	7’	2.1	180000	14	16	0	16	240	No rbc	13	0	-	-	4	12
28	Krishnan	M	38	1005452	U	RA	G1	-	-	3’	3.1	220000	18	28	0	16	220	No rbc	10	0	+	-	3	3
29	Asok kumar	M	40	1008867	U	LF	G1	-	-	4’	2.2	240000	14	16	-	18	260	No rbc	3	0	-	-	15	-
30	Chithravel	M	42	1008873	U	RA	G1	-	-	4’	3.2	300000	14	16	-	-	280	No rbc	5	0	-	-	4	-
31	Vinod	M	7	1003904	U	RF	G2	-	-	ID	3.4	90000	20	40	1-2	30	175	No rbc	10	0	+	-	3	4

32	Eswari	F	7	1005067	U	RF	G1	-	-	12’	0	292000	14	18	0	18	275	No rbc	2	0	-	-	2.5	-
33	Thirumurugan	M	18	995470	U	LF	G3	-	HP	ID	4.1	52000	-	-	-	-	148	No rbc	20	10	-	-	6	10
34	Govindaraj	M	50	996226	U	RF	G3	-	GB	ID	4.1	94000	20	38	.5-1	28	-	Rbc+	11	0	-	-	10	12
35	Karuppayyan	M	38	997940	U	RF	G2	-	-	ID	4.1	88000	18	-	-	-	168	No rbc	10	0	-	-	1	11
36	Anandan	M	19	1000611	S	LA	G3	-	GB	ID	0	120000	-	-	-	-	164	No rbc	20	0	-	-	4	12
37	Chandrasekar	M	26	1000552	U	RF	G2	-	-	ID	2.1	100000	14	38	.5-1	26	210	No rbc	10	20	-	1	3	-
38	Shammugan	M	65	1001379	U	RF	G2	-	-	ID	4.1	99000	20	38	.5-1	40	75	No rbc	10	0	-	-	8	6
39	Paramasivan	M	60	1002250	U	RF	G2	-	-	ID	0	-	21	33	1-2	23	83	No rbc	10	0	-	-	7	4
40	Rajendran	M	40	1002440	K	LF	G2	-	-	ID	2.4	90000	-	-	-	-	194	No rbc	10	0	- -	-	7	10
41	Nagaraj	M	54	1003185	U	RF	G3	SHK	GB	ID	4.1	88000	24	35	1-2	36	110	No	20	0	+	-	-	-
42	Murugesan	M	36	1003156	U	RF	G3	-	HP	ID	0	90000	22	30	.5-1	34	152	No rbc	10	0	-	-	6	12
43	Ganesan	M	39	1004145	R	LA	G3	-	HM	ID	0	110000	20	34	-	30	144	No rbc	10	0	-	-	14	8
44	Vellayan	M	50	1004115	U	RA	G3	-	GB	ID	4.1	80000	22	38	-	34	136	No	10	30	-	2	8	4
45	Shanmugan	M	25	1001530	U	RA	G2	-	-	ID	1.5	100000	20	34	1-2	28	-	No rbc	10	0	-	-	2	4
46	Pugalenthi	M	41	1004063	U	LF	G2	-	-	ID	3.1	110000	22	32	.5-1	34	150	No rbc	15	0	-	-	2	16
47	Punnathidasan	M	30	1004160	S	RF	G2	-	-	ID	4.1	90000	-	-	-	-	170	No rbc	15	0	-	-	8	12
48	Tamilvarnan	M	23	1004165	U	RA	G2	-	-	ID	1.5	110000	24	30	-	30	150	No rbc	10	0	-	-	12	8

ABBREVATIONS

S- serial number **M-** male **F- f**emale **Si-** site **B-**bite **X-**sex

Ip- inpatient number **U-**unknown **K-**krait **R-**russel viper **S-**saw scale viper

LF-left foot **Grd-**grade **RF-**right foot **LA-**left arm **RA-**right arm

G1-grade one **G2-**grade two **G3-**grade three **Syb-**systemic bleed

Epx-epistaxis **Ptos-**ptosis **HM-**hemetemesis **F-**renal failure

P-peritoneal dialysis **HP-**hemoptysis **ID-** in definite **Assf-**associated features

Plt- platelet count in lakhs **Tt-**thrombin time in seconds

Bt- bleeding time in minutes **Ct-**clotting time in minutes

Fdp-fibrin degradation products **Fib-**fibrinogen mg%

UD-urine deposits **Pt-**prothrombin time in seconds

Ap-activated partial thromboplastin time in seconds

Bni-bite needle interval in hours **Aa-**number of ASV given after clotting time normalization

Ab- number of ASV vials given before clotting normalization

Nt- normalization o clotting time in hours after ASV therapy