A STUDY ON THROMOCYTOPENIA AND ALBUMINURIA AS EARLY PREDICTORS OF AKI IN SNAKE BITE

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THROMBOCYTOPENIA AND ALBUMINURIA AS EARLY PREDICTORS OF AKI IN PATIENTS WITH SNAKE BITE

submitted by Dr. SUDHAKARAN. J. **of**

Dept. of GENERAL MEDICINE **Thanjavur Medical College, Thanjavur**

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I solemnly declare that this Dissertation titled **"A STUDY ON THROMBOCYTOPENIA AND ALBUMINURIA AS EARLY PREDICTORS OF AKI IN SNAKE BITE"** was done by me in the Department of General Medicine, Thanjavur Medical College, and Hospital , Thanjavur under the Guidance and Supervision of my Chief **Prof. Dr. C. Paranthakan M.D**., Professor, Department of General Medicine, Thanjavur Medical College and Hospital, Thanjavur between 2015 and 2018.

This Dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University , Chennai in partial fulfilment of University requirements for the award of M.D Degree (GENERAL MEDICINE).

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This is to certify that this dissertation work titled "**A study on thrombocytopenia and albuminuria as early predictors of AKI in snake bite**" of the candidate **DR. J SUDHAKARAN** with registration Number 201511214 for the award of M.D in the branch of General Medicine. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 6% (Six)of plagiarism in the dissertation.

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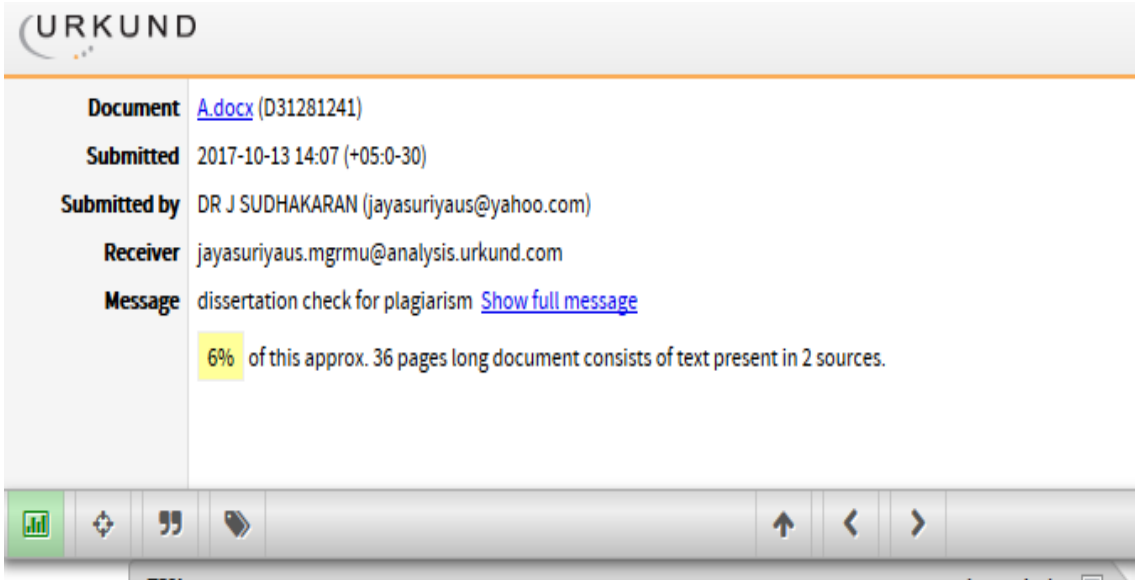
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The hood markings distinguish the cobra from other species, and its habit of rearing up when alarmed make it distinctive but not definitive, as other species do this, notably the Trinket Snake.

On the ventral surface of the hood are faint, broad, black stripes above which are two dark spots that extend over 3 to 4 scales. The head is small, and pupils are round. The most important distinguishing feature of this snake is the fact that the 3rd supralabial shield touches the eye and nose shield. Also, a small wedge-shaped scale ("cuneate") is present between the 4th and 5th infralabials. Another important feature is said to be the presence of 3 small scales just behind each eye. KRAITS: The common krait is a steel-blue snake growing up to 3 to 4 feet in length (sometimes up to 7 feet), with whitish bands or half-rings throughout its back . Occasionally, it may be grey or dark brown in colour. The

markings consist of paired white bands which may be less distinct anteriorly.

The common krait has small dark eyes, and the pupils are almost invisible. The upper lip is white or yellow, while the belly is very white. The most distinctive features comprise the following: A chain of hexagonal large scales throughout the middoral aspect of the body . The subcaudals (ventral scales distal to the vent) are undivided, unlike other elapids. The 4th infralabial scale is the largest of the infralabials. VIPER:

The two species of vipers in India are Russel viper and saw scale viper. Russelviper is a brownish, stout snake, growing up to several feet in length . The head is triangular, with a 'V' shaped mark (apex pointing forward), and is covered with small scales. Pupils are vertical. Fangs are long, channelised, and hinged, being erected at the time of striking .There are 3 rows of chained dark spots over the entire body. The Russell's viper is known to hiss loudly when agitated. Like other vipers, it is viviparous. Russell's viper

ABBREVIATION:

AKI – Acute Kidney Injury

IMCU – Intensive Medical Care Unit

BP – Blood Pressure

PR – Pulse Rate

HR – Haemorrhagin

DIC – Disseminated Intravascular Coagulation

MAHA – Micro AngiopathicHaemolyticAnaemia

RVV – Russells' Viper Venom

ARF – Acute Renal Failure

CaCl2 – Calcium Chloride

CPK –CreatininePhospho Kinase

CK – Congested Kidney

ABG – Arterial Blood Gas

ASV – Anti Snake Venom

AV block – Atrio Ventricular Block

DNA – DeoxyRibo Nucleic Acid

WBCT – Whole Blood Clotting Time

FDP – Fibrin Degradation Product

ATN – Acute Tubular Necrosis

ACN – Acute Cortical Necrosis

RBC –Red blood cells

ABSTRACT

BACKGROUND:

Snake bite is one of the most preventable causes of deaths and the incidence of snake bite is on increasing trend due to various factors. The most serious complication of snake bite is AKI and my study is to assess thrombocytopenia and albuminuria as early predictors of AKI in snake bite.

METHODOLOGY:

Fifty patients who got admitted in Thanjavur Medical College for the period of six months from March 2017 to August 2017 with history of snake bite were taken for study and they were followed with blood urea, serum creatinine urine albumin and platelet count and assess which subset of patients were progressing to AKI and how the detection of albuminuria and thrombocytopenia helps in assessment of progression of cases to AKI.

CONCLUSIONS:

In patients with snake bite ,Albuminuria and thrombocytopenia are associated with development of Acute kidney injury

CONTENTS

1. INTRODUCTION

Snakes are a fascinating part of nature. Their colour movement and secret habits make them more mysterious. India is home to some of the most poisonous snakes in the earth, most of which are located in rural areas.

Venomous snakebites are an important medical problem and occupational hazard in India. Russell's viper is the major cause of snakebite leading to increased morbidity and mortality following acute kidney injury AKI [32]. The annual mortality is around 30,000 most of them from South-East Asia and West Africa.

Approximately, 10,000 deaths occur in India. An incidence of renal involvement with snakebite envenomation of 1.4-28% has been reported in various series,] and incidence of ARF is 10-32%. Among multifactorial cause for the pathogenesis of snakebite-induced AKI[33,63,64,65,66] (SAKI), elevated oxidative, and carbonyl stress (CS) leading cause of kidney injury. Oxidative stress (OS) results in the modification of protein either directly through the oxidation of amino acid residues by reactive oxygen species (ROS) or indirectly by an increased generation of reactive carbonyl species.

Although increased CS and protein modification has been extensively studied in both hyperglycaemic and corticotropin-releasing factor and many cases of AKI[35], proteins damage due to OS and CS in SAKI has not been described well in literature.

Snake bites cause substantial mortality and morbidity in India. Most of the snake bites occur when people are working in bare footed conditions, in the fields or while walking in the night or in the morning along fields and along roads.Superstitions, wrong practises, misconceptions, handicap doctors who care primary attention.

Out of the 3000 species of snakes in the world, 216 species of snakes are found in India and in them 52 species of snakes are poisonous. Our venomous species belong to major families. They are Elapidae and Viperidae.

We observe acute renal failure/acute kidney injury[41] in most of the cases. The gravity, spectrum and outcome varies. Our study is to observe that how many cases with thrombocytopenia and albuminuria progress to acute renal failure/ acute kidney injury[42].

2. AIMS OF STUDY

1. To correlate the association of albuminuria on presentation and acute kidney injury.

2. To correlate the association of thrombocytopenia on presentation and acute kidney injury.

3. To follow up the cases after they progress to acute kidney injury.

3. REVIEW OF LITERATURE

3.1 EPIDEMIOLOGY OF VENOMOUS SNAKES AND SNAKE BITE INDUCED ACUTE KIDNEY INJURY

Snake bite is a preventable health hazard in the tropical regions. Very large scale research is going on due to its high incidence in those areas. It accounts for 125-175 deaths per day in India and the annual deaths per year are around 45000. It is the cause for a major preventable death. In India, the highest incidence is in Tamilnadu,Kerala, west Bengal, Uttar Pradesh and Maharashtra.

Snakebites are reported from virtually every part of the world, except those countries where snakes (especially venomous snakes) are relatively rare. The incidence of serious bites is significantly higher in the tropics than in industrialised nations of the West.

This is exemplified by the fact that while the USA records 6,000 to 8,000 venomous bites per year, with mortality ranging from 5 to 15 deaths, India records about 200,000 bites, of which nearly 15,000 end in death. In Britain, hardly 200 bites are reported each year, and only 14 deaths have occurred in the last 100 years! Epidemics of snakebite have resulted from a sudden increase in snake population density, for example after flooding in Columbia, Pakistan, India, and Bangladesh.

Invasion of the snake's habitat by large numbers of people may also be followed by an increased incidence of snakebite. This occurred during the construction of new roads through jungles in South America, and during the movement of farmers to newly immigrated areas in the former dry zone of Sri Lanka. Among the various states in India, Maharashtra records a high incidence of snakebites—more than 1,000 bites per year. Most of the bites are reported from rural parts of the state.

Other states with significant reportage of snakebites include West Bengal, Uttar Pradesh, Tamil Nadu, and Kerala. Most of the bites are said to be due to saw-scaled viper (almost two-thirds), while one-fourth of the number is due to Russell's viper; cobra, krait, pit viper, etc., account for only a small number of cases. A recent report from South India indicates that nearly 20% of poisoning cases admitted to hospitals could be due to envenomations.

Snake bites happen to farmers when the farmers work in field bare footed unintentionally in a handful of foliage rolling over the snake while asleep , while working in plantation and in those who handle snakes. Males are affected more than females and the lower limbs are the most common sites.

3.2 VENOMOUS SNAKES BELONG TO 5 FAMILIES[46,47]:

1. Colubridae:

This family includes almost 1400 species, or 75% of all the snake genera and 78% of all the snake species in the world. Approximately 400 of these species of Colubridae have short immobile fangs, or enlarged solid teeth at the posterior end of the maxilla. About one third of the Colubrid species possess rear fangs which deliver toxic saliva delivered by a chewing motion. Colubrid snakes are the predominant species on all continents except Australia. Examples include mountain racer, Western and Eastern hognose snakes, parrot snake, rat snake, wandering garter snake, etc.

2. Atractaspididae:

This family comprises African and Middle Eastern burrowing asps or stilleto snakes (also known as burrowing or mole vipers or adders, false vipers, side-stabbing snakes), which have very long front fangs used for immobilising their prey by a side-swiping motion. These fangs often protrude from the corner of the partially closed mouth.

3.Elapidae:

These snakes have relatively short, fixed front (proteroglyph) fangs, which however may extend up to 10 mm long). They are anchored at the anterior portion of the maxilla. Examples include the following— a. Cobras

(Naja) b. Kraits (Bungarus) c. Coral snakes (Calliophis, Maticora, Micrurus) d. Mambas (Dendroaspis)

4. Viperidae:

These snakes have highly developed long curved, hinged, front fangs, which are channelised in the form of a hypodermic needle. There are two sub families— a. Viperinae or true vipers: Vipers and adders b. Crotalinae or pit vipers: Rattle snakes (Crotalus, Sistrurus), and Asian pit vipers (Trimeresurus, Hypnale).

5. Hydrophidae:

This family comprises sea snakes, which have short fi xed fangs as in the case of the elapids. Approximately 330 species of snakes exist in India, of which about 70 species are venomous (40 land snakes and 30 sea snakes). The commonest Indian venomous snakes are referred to as the "Big Four", and comprise common krait (Bungaruscaeruleus), common cobra (Najanaja), saw-scaled viper (Echiscarinatus), and Russell's viper (Viperaruselli) Renal involvement is associated with bites from the last 2 families.

COBRAS:

The common cobra is usually brown or black in colour. It is a distinctive snake growing up to 5 to 6 feet in length, with a distensible neck that can be expanded into a hood. On the dorsal side of the hood, there may be a monocellate

(monocle) or binocellate (spectacle) mark. The former is more common in the Bengal cobra (Najakaouthia).

The monocellate cobra is generally brown or black, with speckled or variegated, white or pale yellow appearance. It often has alternate wide and narrow, transverse, dark bands. Dorsal hood mark is a pale circle edged with black and has 1 to 3 spots; ventral hood mark has a pair of dark spots, or a wide dark band.

Another variety of cobra that is encountered in the Indian sub-continent is the Andaman cobra (Najasagittifera). The hood markings distinguish the cobra from other species, and its habit of rearing up when alarmed make it distinctive but not definitive, as other species do this, notably the Trinket Snake. On the ventral surface of the hood are faint, broad, black stripes above which are two dark spots that extend over 3 to 4 scales. The head is small, and pupils are round. The most important distinguishing feature of this snake is the fact that the 3rd supralabial shield touches the eye and nose shield. Also, a small wedge-shaped scale ("cuneate") is present between the 4th and 5th infralabials. Another important feature is said to be the presence of 3 small scales just behind each eye.

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VIPER:

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The saw-scaled viper is a small snake, about 1½ to 2 feet long, and is usually brown in colour . Occasionally, the colour appears greenish. There is a wavy white line along the entire length of each flank, while diamond-shaped markings extend over the back, numbering usually 25 to 30. The head is triangular with small scales.

A characteristic whitish, arrow-shaped or crow's foot mark is often present on the head. The pupils are vertical. The saw-scaled viper is named as such because its scales are serrated. When agitated, it throws itself into a double coil (in the manner of a "figure of eight"), and rubs the coils together vigorously, producing a harsh, rasping sound, akin to the sound of a sandpaper being scraped over a rough surface. At the same time, it also hisses loudly by exhaling forcefully through the nostrils. Like other vipers, the saw-scaled viper is viviparous. The echis is an aggressive snake and may bite on the slightest provocation.

The family Viperidae includes adders, pit vipers (like rattlesnakes, cottonmouths and copperheads), the Gaboon viper, green vipers and horned vipers.

All vipers are venomous and have long, hinged fangs.

Name	Origin
dehydrogenase lactate	Elapidae
L-amino-acid oxidase	All species
Catalase	All species
Alanine amino transferase	
Phospholipase A_2	All species
Lysophospholipase	Elapidae, Viperidae
Acetylcholinesterase	Elapidae
Alkaline phosphatase	Bothrops atrox
Acid phosphatase	Deinagkistrodon acutus
5'-Nucleotidase	All species
Phosphodiesterase	All species

3.3 SNAKE VENOM:

Snake venom[48,49,50] is a special form of saliva that contains a range of zootoxins and is stored in something akin to our salivary gland. Once the venom is created and stored in these glands, it does not move back through the body, where it could infect other tissues, just as it does in their prey. The toxic venom is stored in these specially protected glands until it is moved down through narrow tubules in the fangs and delivered into the snake's prey.

PHOSPHOLIPASE A:

Phospholipase A1 is a phospholipase enzyme which removes the 1-acyl. Phospholipase A1 is an enzyme that resides in a class of enzymes called phospholipase that hydrolyze phospholipids into fatty acids. It has a direct lytic and hemolytic effect and hydrolysis of phospholipase of RBC membrane and causes a sudden decrease in BP.

CHOLINESTERASE[51]:

It is either of two enzymes that catalyze the hydrolysis of these cholinergic neurotransmitters, such as breaking acetylcholine into choline and acetic acid. It is found in cobras. It hydrolyses acetylcholine to cholic acid and acetic acid.

ACETYL CHOLINE-COBRA-CROTALIDAE

Acetylcholine (ACh) is an organic chemical that functions in the brain and body of many types of animals, including humans, as a neurotransmitter[52].It has a direct action on the heart and the neuromuscular junction.

PROTEINASE:

Markedly present in vipers, Crotalidae. It leads to tissue damage and destruction.

ANTI COAGULANT:

It has anti coagulant effect because of proteolytic disintegration of fibrinogen.

COAGULANT EFFECT:

It has coagulant effect by converting Prothrombin into thrombin.

NON ENZYMATIC COMPONENTS:

Haemorrhagins (HR 1 AND HR 2) has direct action on endothelium containing procoagulant and anticoagulant effects . It causes very fast haemorrhage continued by vasodilatation of micro vessels, haemorrhages .

3.4 PATHOGENESIS OF ACUTE KIDNEY FAILURE:

The exact pathogenesis of acute kidney failure is not correctly known, due to lack of animal models. The factors contributing are Direct cytotoxicity , bleeding , Hypotension, intravascular haemolysis ,DIC, microangiopathic haemolytic anaemia.

Oligoanuria and bleeding manifestation were the most common clinical manifestation. Besides this hypotensive shock, cellulitis or feature of severe inflammation and regional lymphadenopathy also observed. Among unusual presentation about eight patients had herpes labialis and two patients had panhypopituiterism.

Herpes labialis in SAKI[41] patients was attributed to a possible immunologically altered state in those patients. Between the two cases of hypopituitarism one case presented during the hospital stay and another case was diagnosed on a subsequent visit with deficiencies of gonadal, steroid, and thyroid axes. They showed marked improvement after replacement of anterior pituitary hormones. The probable mechanism was thought to deposition of fibrin microthrombi and hemorrhage in the pituitary gland resulting from the action of venom procoagulant enzymes[54] and hemorrhagin.

DIRECT NEPHROTOXICITY:

The pathogenesis of renal lesions is multifactorial and has been attributed to the nephrotoxicity of venom, hypotension, circulatory collapse, and intravascular hemolysis with hemoglobinuria, myoglobulinuria, DIC, hemolytic uremic syndrome, sepsis, and other factors such as hypersensitivity to venomous or antivenomous protein. Pathological investigations of human fatal cases revealed renal cortical necrosis, distal nephron nephrosis, thrombotic microangiopathy, and acute tubular necrosis.

Experiments with I-125 labelled E. carinatus venom and venom antigen in human victims have shown that the venom is excreted in the urine, without essentially causing damage to the kidneys. There were slight changes in the beta N-glucosaminidase in patients bitten by Russells viper, without DIC, showing a direct toxic effect on renal function.

In a study, the administration of lethal dose of Russells' viper or E.carinatus in rhesus monkey showed hemorrhages in kidneys and other organs and mild ATN in 20percent animals inside 24hrs. After a sub lethal dose more than 50percent animals developed ATN. Fibrin thrombi was seen in 50-75 percent of glomeruli. The histological findings and the coagulation abnormalities seen in the animals were similar to the human victims.

The strongest evidence is dose dependent reduction in Inulin clearance and increase in fractional excretion of sodium in the isolated perfused rat kidney due to russells viper venom. But this didntincluse morphological analysis of the kidneys. To obtain more information about direct toxicity in renal tissue ,Willinger et al studied combined functional and morphological changes in perfused rat kidney and complimented the studied in renal epithelium and mesangial cell cultures.

RVV Administration caused changes in the renal plasma flow, glomerular filtration rate, filtration fraction and tubular reabsorption of sodium were reduced and fractional excretion of sodium and water increased. Both oliguria and subsequent polyuric phase was shown. On morphological analysis, the prominent pathology was in renal cortex. Extensive damage and loss of glomerular epithelial cella and endothelium was detected by basement membrane remaining. Ballooning and even rupture of glomerular capillaries was visible.

Another prominent feature of RVV is its action on renal cortex and other zones along with its concerned vessels and muscle walls. The venom led to the complete lysis of the vascular smooth muscle layer of muscle cells. Only the basement membrane was left behind. There were different degrees of epithelial injury in all tubular segments.

In cell culture studies, RVV caused a complete destruction of confluent mesangial cells at lower concentration. In epithelial cell cultures, only higher doses caused discernible damage. Willinger et al thus demonstrated a direct dose dependent toxic effect of RVV on isolated perfused rat kidney, mostly against glomerular and vascular structures and on mesangial cells.

In addition to that , myoglobinuria, sepsis and hypersensitivity to venomous or anti venomous protein may also lead to renal failure. Crescentic nephritis in patients who were bitten by puff adder also showed hypersensitivity to antisnake venom. Myoglobinuria usually occurs following a sea snake envenomation which leads to necrosis of striated muscles and muscular paralysis.

HYPOTENSION:

Bleeding either into the tissues or external bleeding or loss of plasma into the bitten area can lead to hypotension and circulatory collapse. It is due to venom metalloproteinases that leads to degradation of the basement membrane proteins surrounding the vessel wall, leads to loss of integrity. Heamorrhagic toxins have been isolated from venom of several snakes Viperidae and Crotalidae families. Hypotension is due to bradykinin release. In addition to that vasodilation and increased capillary permeability. Both as a result of direct and indirect effects of venom can aggravate the circulatory disturbances of shock. Viperapalestinae

venom causes shock by depressing the medullary vasomotor center. Bitisarietans causes hypotension byreducing myocardial activity , arteriolar vasodilation and increase of vascular permeability. Irrespective of the cause , hypotension and circulatory collapseresults in ischemic ARF.

INTRAVASCULAR HEMOLYSIS:

Another factor that have pathogenetic importance in snake bite induced ARF is intravascular hemolysis. Hemolysis results due to phospholipase A2 which is found in almost all snake venoms[55,56] and 'direct lytic factor' found only in elapid venoms. Phospholipase A2 leads to hemolysis by direct hydrolysis of RBC membrane phospholipids or indirectly by the production of lysolecithin which has strong haemolytic effect from plasma lecithin.

Evidence of intravascular hemolysis by anemia,jaundice, reticulocytosis, raised plasma free HB, abnormal peripheral blood smear , present in 50percent by Russells viper and E.carinatus. In a study , using male wistar rats , severe hemolysis leads to increase in plasma LDH levels, free hemoglobin and late presence of hemolysed RBC casts in renal tubules after envenomation of Bothropsjararaca.

Certain people have said that renal failure after a snake bite should be considered as HUS. However, while intravascular hemolysis is frequently observed, microangiopathic hemolysis is seen only rarely in hemolytic uremic syndrome. More than 70-80percent patients with snake bite induced renal failure only have ATN and they do not show glomerular and arteriolar changes which are characteristically associated with HUS.

DISSEMINATED INTRAVASCULAR COAGULATION:

The human hemostasis[14] is kept in balance by a number of crucial interactions between blood proteins, platelets, endothelial cells and subendothelial structures. Snake venom proteins and peptides are commonly involved in activating or deactivating these interactions. Snake venoms mainly from viper and pit viper families have proteins that acts on members of the coagulation cascade and the fibrinolytic pathway.

Russells viper venom(RVV) contains a factor V activating serine proteinase, which is seperated from X activating protein also present in this venom. The enzyme (RVV-V) is a single chain glycoprotein which has a molecular weight of 26,100 possessing one glycosylation site near the carboxy terminal. RVV-V cleaves a single peptide bond to convert factor V to Va. Russells viper venom also has a potent activator of human coagulation factor X[18] .Factor X activators have been isolated from Bothropsatrox and several

other snakes. Russells viper venom also activates factor IX by cleavage of a single peptide bond results in the forming of factor IXa.

There are several prothrombin activators in snake venom. The activity of group I members is not influenced by components of prothrombin activating complex. Ecarin from E.carinatus venom is the most studied member. Group II activators resemble factor Xa cleaves peptide bonds in prothrombin. It leads to active 2-chain thrombin. It is strongly stimulated by phospholipids and factor Va in the presence of CaCl2.These enzymes are present in all venoms of Australian elapid snakes and the best one is from the tiger snake.

In contrast to that , the activators of group III only requires phospholipid and CaCl2 for the prothrombin activation. They do not require factor Va but seem to have a co factor slightly similar role which is tightly bound to Catalytic subunit . This class of activator is seen in Australian elapids and is represented by aHMWactivator from Taipan venom.

Eventhough thrombin has several activities , some Snake venoms have the ability to clot fibrinogen and so called thrombin like. These are mostly found in venom of snakes from true vipers like Bitisgabonica. The fibribogen clotting enzymes of snake venom have been classified into fibrinopeptidases A and B from fibrinogen.

One mechanism of snake venom proteins having anticoagulant action is attributed to protein C activation . Activated protein C degrades factors Va and VIIIA and therefore it has anticoagulant activity . Another mechanism of anticoagulation involves inhibition of coagulation of blood by factors like IX and X by the proteins from venom that binds to either or even both. At the end, anticoagulation is achieved by the action of the phospholipases[58,59,60] from snake venom. It degrades the phospholipids that are involved in the formation of complexes that are very crucial for activating coagulation pathway.

The enzymes that causes fibrinolysis have been isolated from the venom of a number of North and South American snakes that include rattlesnakes and copperheads from elapids like cobras and European vipers. The venom fibrinolytic enzymes classified are zinc metalloproteinases as alpha and beta chain fibrinases. They contain a number of platelet active components that cause platelet aggregation and those that inhibits platelet aggregation.

The final coagulation depends upon the balance between the procoagulant, anticoagulant, fibrinolytic and fibrinogenolytic components of venom. DIC is a feature in patients who are bitten by Russell's viper, E.carinatus, and pit vipers. The DIC Is a major hemostatic abnormality is well recorded. The infusion of Russell's viper or E.carinatus venom into a rhesus monkeys lead to abnormal coagulation profile which suggests DIC within

2hours of injection of lethal dose of venom, but these changes occurred few weeks after sub lethal envenomation.

The presence of fibrin thrombi in the renal microvasculature and in the glomerular capillaries , and the records of MAHA and thrombocytopenia[7] in patients with necrosis of cortical tissues. It strongly suggests that DIC plays a major role in cortical necrosis induced by snake bite. It initiates a reaction which involves coagulation ,fibrinolytic , kinin and complement systems. The alterations that are induced by venom leads to coagulation and to fibrin thrombi deposition in vessels. The fibrin deposition which is intraglomerular of lesser degree is being suspected as causing ATN via transient hemodynamic change.

The role of factors that cause ARF was shown in an experimental model by Burdmann et al. They injected 0.4mg/kg of Bothropsjararaca venom intravenously into male Wistar rats . It produced morphological and functional changes that are similar to those observed in human snake bite induced ARF.There was an acute and sjgnificant reduction in the GFR, urine output , renal plasma flow and serum fibrinogen levels. It causes intravascular hemolysis and it shown by a significant decrease in hematocrit and an increase in plasma LDH levels and free hemoglobin . The microscopy showed massive fibrin deposition in glomerular capillaries apart from the proximal and distal tubular necrosis and RBC cell casts in renal tubules. In this model, ischemia that

is related to glomerular coagulation and intravascular hemolysis were the major factors that causes a decrease in the GFR , although direct venom nephrotoxicity could not be excluded.

3.5 SIGNS AND SYMPTOMS [4]:

Venomous Snakebite

1. Without Envenomation:

a. It is well known that even when a highly venomous snake bites a human, serious envenomation may not occur. In fact, it has been suggested that 20 to 50% of venomous bites are not attended with serious toxicity.

b. Reasons for lack of envenomation in venomous bites include the following:

- Dry bite: A snake does not always inject venom at the time of biting.
- Protective gear: Envenomation may not occur in the case of bites inflicted on shod feet or heavily clothed parts.
- Leakage of venom: Head-on bites often result in efficient injection of venom, while sideswipes may cause some (or all) of the venom to escape outside the bitesite.
- Superficial bite: Since humans do not constitute normal prey for most venomous snakes, they bite only to defend themselves before making a quick get-away. In such instances, the snake often deliberately does not bite deeply,

but instead only strikes superficially, thereby conserving precious venom for its genuine prey.

2. With Envenomation:

a. Colubrid bite

 Clinical effects of colubrid snakebite are generally localised, and comprise pain, oedema, erythema, ecchymosis and numbness, which resolve over one to two weeks.

 Excessive salivation with metallic taste, and headache have also been reported.

b. Elapid bite

 Local Effects: In general, elapid bites are associated with minimal local manifestations . Pain and swelling are relatively less intense, and often there is only a serosanguinous ooze from the bitesitewith mild pain, tenderness, and blistering. However, cobras can occasionally cause significant local swelling, blistering, and regional lymphadenopathy. The lesion may emit a putrid smell, and break down with loss of skin and subcutaneous tissue .Elapid bites sometimes cause early onset of gangrene (of the wet type), while viperid bites progress more slowly, and the gangrene is usually of dry type. Secondary infections, e.g. tetanus, gas gangrene, etc. are relatively less common.

 Systemic Effects: Neurotoxicity is the dominant clinical feature of elapid bites. Symptoms usually occur earlier (within 15 minutes to ½ hour) in cobra bite, while they are often delayed (up to several hours) in krait bite. – Preparalytic Stage— - Vomiting -Ptosis (preceded by contraction of frontalis muscle) -Blurred vision, external ophthalmoplegia - Paraesthesiae around the mouth - Hyperacusis -Headache, myalgia - Vertigo -Hypersalivation (due to autonomic stimulation). –

Paralytic Stage— - The facial muscles, palate, jaws, tongue, vocal cords, neck muscles, and muscles of deglutition all become progressively flaccidly paralysed. Many patients find it difficult to open their mouths and speak. - Respiratory arrest may occur due to obstruction of upper airway by the paralysed tongue or inhaled vomitus, or due to paralysis of intercostal muscles and diaphragm. Paradoxical respiration, as a result of the intercostal muscles becoming paralysed is said to be a frequent sign. -Although a patient appears unconscious, most are able to follow simple commands as noted by purposeful movement of the fingers or toes. Loss of consciousness and convulsions are terminal phenomena resulting from hypoxaemia. -Roughly half of patients bitten by Najakaouthia (monocellate cobra) do not sustain envenomation. Local pain and swelling develops within 2 to 3 hours and becomes maximal in 24 to 48 hours. Blisters and skin discolouration may develop, and may be followed by necrosis of subcutaneous tissue with sloughing. Neurotoxicity, if it develops,

generally begins 1 to 5 hours after envenomation, but may be delayed as long as 19 hours. Cranial nerve palsy is followed in some patients by generalised weakness and respiratory failure. - Renal complications are rare in elapid bites. - Although rarely reported in literature, disorders of platelet aggregation and coagulation-fibrinolysis system may occur after envenomation by cobras. Disseminated intravascular coagulation (DIC) may occur after bites by these snakes. -Coral snakes usually cause milder manifestations as compared to other elapids. Even substantial envenomation is associated with full recovery, following timely intervention.

c. Viperid bite

 Local Effects: –Pitless as well as pit vipers cause marked local manifestations which develop rapidly, usually within ½ hour, but may occasionally be delayed for several hours. – Swelling first appears around the bite site, and then spreads quickly to involve the whole limb and adjacent trunk. There is associated pain, tenderness, and regional lymphadenopathy. Bruising is commonly seen over the path of superficial lymphatics and over regional lymph nodes. Persistent bleeding from bite site is a constant feature. –Blisters begin to appear in about 12 hours in and around the bite site, progressing subsequently to involve the entire limb. They may contain either clear or bloodstained fluid. In about 10 to 15% of the cases, extensive necrosis of skin, subcutaneous tissues, and muscles may occur. –Raised intracompartmental pressure adds to the problem in

regions with tight fascial compartments such as anterior tibial compartment. This is characterised by severe pain, tense swelling, subcutaneous anaesthesia, and increased pain on stretching intracompartmental muscles.

 Systemic Effects: –Haemostatic abnormalities are very characteristic of viperid bites. The first evidence of this is persistent bleeding from the bitesite. Haematuria may be seen within a few hours of the bite . Later gingival bleeding occurs , followed by epistaxis, haemoptysis (relatively rare), haematemesis, ecchymoses, intracranial and sub-conjuctival haemorrhages, and bleeding into the floor of the mouth, tympanic membrane, gastrointestinal tract, and genito-urinary tract. Bleeding into anterior pituitary (causing a Sheehan-like syndrome) has been reported. Subarachnoid haemorrhage manifests as severe headache and meningism, while intracerebral haemorrhage may cause hemiplegia, loss of consciousness, and convulsions. Retroperitoneal and intraperitoneal haemorrhages cause abdominal distension, tenderness, and peritonism, with signs of haemorrhagic shock.

Viperid envenomation is almost synonymous with incoagulable blood, which results from defibrination. Intravascular haemolysis causing haemoglobinuria and renal failure [(62)]is a frequent occurrence, especially in bites by Russell's viper. Acute renal failure is often associated with the presence of DIC which results in severe renal tubular and cortical necrosis with widespread microvascular fibrin deposition (microthrombi). It is suggested, however, that a

direct toxic effect produced by the venom of Russell's viper may produce renal damage. The hump-nosed pit viper can also cause renal failure, but the saw-scaled viper usually does not. – Hypotension is an important manifestation in all viper bites and is usually accompanied by tachycardia, unless the venom has affected the heart directly or reflexly, in which case the pulse may be slow or irregular. – A study on saw-scaled viper bites has indicated that haemorrhagic manifestations could more commonly be due to primary pathological fibrinolysis (PPF) than disseminated intravascular coagulation (DIC). The significance of this assertion is that administration of heparin which is the treatment of choice for DIC, may actually worsen the condition if it is due to PPF. – Cardiotoxicity[9] (which may be seen in elapid bite also) produces a wide variety of ECG changes. It is important to note that ptosis and neurological symptoms[5] may occur in the case of Russell's viper bite , and every clinician must be alert to this possibility. Generalised flaccid paralysis can develop after envenomation. Neurotoxic effects are caused by the presence of phospholipases A2 with presynaptic neurotoxic activity. Conversely however, kraits and cobras do not cause coagulation abnormalities.

d. Hydrophid bite

 Local Effects: Sea snakebites are well-known to produce minimal local effects. The bite itself is often painless and the victim may not even realise he has been bitten. However teeth are often left behind inthe wound. Local

swelling is negligible, and regional lymphadenitis usually does not occur. Fang marks may appear as one, two or more small circular dots, as though made by a pin or hypodermic needle. It is important to note that in some cases, there may be no clear fang marks, but a vague scratch mark, and yet serious poisoning may occur.

 Systemic Effects: –The dominant clinical feature is myalgia with stiffness and tenderness of muscles, which become apparent in ½ hour to 2 hours. This is due to rhabdomyolysis, since hydrophid venom is predominantly myotoxic. Myoglobinaemia and myoglobinuria occur, resulting in acute tubular necrosis and renal failure. A "fixed" specific gravity of 1.010–1.013, together with a low urine volume output, myoglobinuria[(12)], and progressively rising blood urea are indicative of impending acute renal failure in the setting of sea snake envenomation. –Trismus is an early feature. Passive stretching of muscles is painful. Later, flaccid paralysis develops, beginning with ptosis (as in elapid bite). –Hyperkalaemia may be present due to release of potassium from damaged muscles. This may be severe enough to cause cardiac arrest. Tall, peaked T waves and QRS prolongation suggest severe hyperkalaemia. –Other effects may include dizziness, nausea, vomiting, headache, and diaphoresis. –Neurotoxicity may include ptosis, ophthalmoplegia, dysarthria, blurred or double vision, mydriasis, inability to sit unassisted, depressed muscle stretch reflexes, and flaccid paralysis. In some cases, paralysis of respiratory muscles

causes death due to respiratory failure. Consciousness is usually retained till the end. The fatality rate is estimated to be about 3%. Failing vision is considered to be a terminal sign.

REGIONAL SYMPTOMS AND SIGNS IN THE BITTEN PART:

The signs include fang marks, local pain, local bleeding, bruising, lymphangitis, lymph node enlargement, inflammation, blistering, local infection, abscess formation, necrosis. A valuable sign of viper bite is local swelling and bite marks and deeper especially in viper bite. Local swelling rarely occurs with Asian Cobra bite.

3.6 GENERALISED SYMPTOMS AND SIGNS:

GENERAL:

It may include nausea, vomiting, abdominal pain, weakness, drowsiness, and prostration. Fright reaction that may develop in patients and it must be differentiated from neurotoxicity.

CARDIOVASCULAR:

It is mainly seen in patients bitten by a Viper. It may include collapse, hypotension, shock, cardiac arrhythmias, coronary vasoconstriction, pulmonary edema and cardiac arrest.

Common ECG changes in snake bite :

Sinus bradycardia ,Sinus tachycardia ,Sinus arrhythmia, Tall T waves , ST depression %1mm with fl at or inverted T in all chest leads , ST depression %1mm with T inversion in inferior leads, or in anterior leads, ST elevation in leads V1 to V6, I, aVL, Q wave V1 to V4 and ST depression in II, III, aVF First degree or second degree heart block.

NEUROLOGICAL:

Neurotoxicity may include ptosis, ophthalmoplegia, dysarthria, blurred or double vision, mydriasis, inability to sit unassisted, depressed muscle stretch reflexes, and flaccid paralysis. In some cases, paralysis of respiratory muscles causes death due to respiratory failure. Consciousness is usually retained till the end. Failing vision is considered to be a terminal sign.

MUSCULAR BREAKDOWN:

It is seen in usually patients bitten by sea snake. They develop generalised pain, stiffness, tenderness of muscle ,trismus, hyperkalemia ,cardiac arrest and acute renal failure.

RENAL:

It develops in patients bitten by the snakes belonging to families Viperidae and Hydrophidae family. Patients usually manifest with loin pain, hematuria, hemoglobinuria ,myoglobinuria, oliguria and also symptoms of uremia. Ischemia occurs due to hypotension and DIC and nephrotoxic effect of

the venom. Pigment nephropathy is also associated with rhabdomyolysis and intravascular hemolysis which leads to ATN . It may also lead to cortical necrosis and renal failure which is usually caused by Russells viper.

HEMORRHAGE AND HEMOTOXICITY:

Haemostatic abnormalities are very characteristic of viperid bites. The first evidence of this is persistent bleeding from the bitesite. Haematuria may be seen within a few hours of the bite . Later gingival bleeding occurs , followed by epistaxis, haemoptysis (relatively rare), haematemesis , ecchymoses, intracranial and sub-conjuctival haemorrhages, and bleeding into the floor of the mouth, tympanic membrane, gastrointestinal tract, and genito-urinary tract. Bleeding into anterior pituitary (causing a Sheehan-like syndrome) has been reported. Subarachnoid haemorrhage manifests as severe headache and meningism, while intracerebral haemorrhage may cause hemiplegia, loss of consciousness, and convulsions. Retroperitoneal and intraperitoneal haemorrhages cause abdominal distension, tenderness, and peritonism, with signs of haemorrhagic shock.

ENDOCRINE:

In acute phase conditions patients develop hypoglycemia and shock. In chronic phase they may develop weakness, loss of secondary sexual hair, amenorrhoea, testicular atrophy, hypopituitarism.

LONG TERM COMPLICATIONS:

Due to loss of tissue by sloughing and surgical debridement at the site of bite , it results in chronic ulceration, infection, osteomyelitis, arthritis which may persist causing physical disability. There may be malignant transformation in skin ulcers after several years.

In Russell's vipers bite, there occurs CRF after bilateral cortical necrosis and chronic panhypopituitarism and diabetes insipidus. In patients who suffered intracranial hemorrhages , chronic neurological deficits are seen.

3.7 PATHOGENESIS OF AKI [45] IN SNAKE BITE:

RENAL HISTOLOGY:

Renal histology mostly shows either an acute tubular or cortical necrosis. Sevaral glomerular changes have also been described but their significance is unknown.

ACUTE TUBULAR NECROSIS:

It is the most common lesion in 70-80 percent of patients with ARF. The tubules appear dilated and lined by flattened epithelium on light microscopy. In severe cases there is cell necrosis and desquamation of necrotic cells from basement membrane. In tubular lamina, hyaline granular and pigment casts are seen. Different degrees of interstitial edema, heamorrhage and

inflammatory cell infiltration are present. Regenerating tubular epithelium were revealed in tubular epithelium. Usually intrarenal blood vessels are not affected.

Proximal tubules show dense intracytoplasmicbodies representing degenerating organelles or protein resorption droplets on ultrastructural examination. Small areas are denuded on the basement membrane. There are several dilated endoplasmic reticulum and many degenerating organelles in the distal tubular cells. Apoptosis indicates a high cell turnover and it is a prominent feature. The fibroblasts seem to be active in the interstitium. They have increased number of organelles and cytoplasmic processes. Mast cells as well as Eosinophils show partial degranulated and granulated forms.

Eventhough the blood vessels appear normal under light microscopy, ultrastructural abnormalities were noticed in both large and small caliber vessels. Medullary vessels are severely affected with markedly swollenendothelial cells with focal necrosis obliterating the lumen. The smooth muscle cells have cytoplasmic vacuoles which maybe empty or filled with granular material. The severe vascular lesions, distal tubular apoptosis and presence of mast cells, eosinophils, active fibroblasts in the interstitium are some of the features which have not been seen in ATN due to other causes.

ACUTE CORTICAL NECROSIS:

In the bites of E.carinatus there may be bilateral diffuse or patchy cortical necrosis. It is more common in Indian patients than among patients in Thailand for reasons unknown. The prominent feature in these patients Is the presence of fibrin thrombi. A narrow subcapsular rim of cortex escapes necrosis. The area under this shows glomerular and tubular necrosis. The necrotic zone is bordered by an area of hyperemia and leukocytic infiltration. There may be calcification of the necrotic areas in later stages. The numbers of glomeruli spared are varying in patients with patchy cortical necrosis. As it heals fibroblastic proliferation and organisation of the thrombi are seen. Renal ultrastructure in cortical necrosis is studied in two patients bitten by Russell's viper.

In one patient, there was glomeruli with collapsed capillary basement membrane and denuded foot processes in a biopsy taken after 10days of bite. No viable mesangial or endothelial cells was identified but certain swollen cells were seen .They maybe of endothelial origin. Necrosis of peritubular capillaries and endothelial swelling of small arterioles were present. In the second patient, the urinary space contained unidentified cells which had large cytoplasmic vacuoles. They were found in the biopsy done after 31days. The tubular basement membrane was thickened and the cortical tubules were lined by flattened epithelium, with large nuclei and a dilated endoplasmic reticulum. There was also fibroblastic proliferation in the interstitium.

GLOMERULAR LESIONS:

Its still a controversial whether or not specific glomerular lesions occur. Proliferative glomerulonephritis was reported in patients bitten by E.carinatus by Sand and Purandare. After that Seedat et al reported two patients with crescentic glomerulonephritis due to puff adder bites presenting as acute renal failure. These workers ascribed these lesions to an allergic reaction to snake venom because renal lesions of proliferative nephritis with crescents had developed within 24-48hrs. Two patients with crescentic glomerulonephritis were described by Sitprija and Boonpucknavig after Russell's vipers bite. In a study with 38patients who were bitten by green pit viper or Russell's viper, thickening of the mesangial areas and mild mesangial proliferation were observed in most of the patients by the authors. They also observed diffuse glomerular hypercellularity. Other observed glomerular changes are endothelial swelling, ballooning of capillaries, mesangiolysis and splitting of glomerular basement membrane . But however the importance is difficult to understand. IgM, C3 and fibrin deposits were seen in immunofluorescence microscopy. In some cases, a diffuse and intense mononuclear cell infiltrate has been noted in the interstitium, which suggests acute interstitial nephritis.

MANAGEMENT:

Immediately after the bite, first aid treatment is carried out either by the patient or someone else. Certain methods like cauterisation, incision, excision, suction

by mouth, vacuum pumps, chemical application, cryotherapy, electric shock have been rejected. Bandage application is not advised due to lack of proper techniques and increased local effect of venom if brought late and ineffectiveness of the bandage, if the bitten limb is mobilized. It should be splinted after bite. Upper limb also should be splinted in a gravity neutral position at the level of heart.

Rapid clinical assessment regarding the airway, breathing and circulation after the patient reached the hospital. Level of conciousness should be assessed. When the patient presents with a shock urgent intervention should be done. It is done even for cardiac arrest precipitated by hyperkalemia, septicemia and renal failure.

The wounds should be cleaned and for under immunised and non-immunised patients, administration of tetanus toxoid or tetanus immune globulin should be considered.

Venous blood should be drawn from an unaffected extremity in a dry, small vessel and they should be given intra venous fluid. The blood is left undisturbed for 20minutes at room temperature. After that the vessel is tilted and the blood is uncoagulated which proves that it is viperine species bite and rules out Elapids. Then the blood is sent for complete blood count, peripheral smear, liver function test , blood urea, serum creatinine, CPK and ABG.

In systemic envenomation, neutrophilia is seen. Heamoconcentration is present due to capillary permeability and thrombocytopenia[6] in viper bite. Hematocrit is decreased due to blood loss or intravascular hemolysis. When MAHA is present and plasma is pinkish in hemoglobinemia and myoglobinemia, fragmented RBCs are seen in peripheral smears.

There is acidosis and blood urea, serum creatinine are elevated when renal failure develops. Proteinuria and hematuria is seen in urine. Evidence of hyperkalemia, ST-T changes, AV block are seen n electrocardiogram ,and chest X ray shows pulmonary edema, pneumonia, pulmonary patchy opacities. It is due to alveolar hemorrhages due to viper bite. Enzyme immunoassay methodology (IgG-based sandwich ELISA and indirect competitive inhibition ELISA) has been optimised for the detection of cobra and krait venom.

3.8ANTI VENOM TREATMENT:

Anti venom is immunoglobulin purified from serum or plasma of a horse or sheep that has been immunised with venoms of one or more species of snakes. Only polyvalent ASV is available in India and it neutralises venom of 4important snakes in India; namely Cobra, Common Krait, Russell viper and saw scaled viper. Though many researches, preparing ASV by human recombinant DNA technology is still not successful.

INDICATIONS FOR ASV:

Reid's criteria (modified by Persson) for antivenom therapy are as follows: Prolonged or recurring hypotension, Persistent or recurring shock in spite of treatment, Pronounced leucocytosis, Protracted gastrointestinal symptoms, Acidosis, ECG changes, Raised serum creatine phosphokinase, Early extensive swelling in adults, Haemolysis, Pregnant women, small children.

Before emerging out with an anti venom it is safe and desirable to wait for clear evidence of systemic envenomation. Allergic reactions occurs in 15% of patients, although fatal anaphylaxis rarely occurs. A matter of controversy is that skin test with horse serum because it delays therapy and itself causes anaphylaxis and serum sickness and has been demonstrated to have a 10 to 36percent false-negative rate and a 33percent false positive rate.

When hemostatic abnormalities are there ,ASV is given. They are spontaneous systemic bleeding, prolonged 20min WBCT, thrombocytopenia[(13)], and elevated FDP or D dimer neurotoxic signs like ptosis, external opthalmoplegia and paralysis , cardiovascular abnormalities like hypotension, shock, heart failure and pulmonary edema. It is given by supporting lab evidences of systemic envenoming and generalised rhabdomyolysis, Acute renal failure and signs of local envenomation. Speed of swelling indicates the severity of local swelling for ASV administration.

All the patients in whom ASV is indicated should receive it. Care should be taken of previous ASV allergy and history of atrophy. They should receive S/C adrenaline, IV anti histamines and steroids.

3.9 DOSES AND ADMINISTRATIONS:

1. Two methods of antivenom administration are recommended:

   IV injection: 2 ml/ minute IV infusion or 5–10ml of isotonic fluid/kg body weight

2. Haemotoxic/Neurotoxic Envenomation (< 3 hrs since bite): 10 Vials ASV

3. Haemotoxic/Neurotoxic Envenomation (> 3 hrs since bite): 7 Vials ASV

No further antivenom is given over the next five hours

Storage of antivenom—Antivenom must be stored in a refrigerator. Lyophilised antivenoms stored at below 8ºC usually retain their activity up to 5 years or more. Reconstituted solutions remain stable up to 48 hours. Diluted solutions should be used within 12 hours of dilution.

Several anti snake venom preparations are available internationally. In India, ASV producers belong to both Public as well as Private sector.

ASV should be given as early as possible and if it is delayed more than 2hrs it will not reverse the local effects of the venom. Once initial dose is administered no further ASV is given for 6hrs.

20 WBCT test every 6hrs will determine if additional dose of ASV is required. ASV may be repeated till the coagulation profile is corrected. But patients who continue to bleed briskly, initial dose of ASV is repeated within 1 to 2hrs.

METHODS OF ADMINISTRATION:

It can be given IV at the rate of 2ml per minute or diluted in 100ml normal saline and given over 1hr. As the half life of Indian ASV is around 90hr, there is no requirement to extend the administration period. Local administration at the bitten site is not recommended.

RESPONSE TO ASV:

If adequate dose of ASV has been given that the patient feels better. Nausea, headache, generalised ache disappears. Spontaneous systemic bleeding stops in 15 to 30mins .Blood coagulability restored in 3 to 9hrs as measured by 20min WBCT. Shock improves in first 30 to 60mins and arrhythmias may resolve. Neurotoxic symptoms begin to improve as early as 30mins. Active hemolysis may cease within a few hrs and urine returns to normal.

ASV Reactions:

Early (anaphylactic) reaction: Develops in 10 minutes to 1 hour of beginning the antivenom therapy. It begins with cough, urticaria, tachycardia, palpitations, nausea, vomiting, headache, and fever. The full-blown anaphylactic reaction is characterised by hypotension, bronchospasm, and angioedema. Treatment involves administration of adrenaline subcutaneously, 0.5 to 1 ml of 0.1% solution (1 in 1000) for adults; 0.01 mg/kg for children. This is followed by an antihistamine (e.g. chlorpheniramine maleate, 10 mg in adults; 0.3 mg/kg in children). - Pyrogenic reaction: Develops in 1 to 2 hours of beginning the therapy. It is characterised by chills, goose fleshing, shivering, rise in temperature, sweating, vomiting, and diarrhoea. Treatment involves fanning, tepid sponging, hypothermia blankets, or antipyretic drugs such as paracetamol (5 mg/kg orally, as suppository, or via nasogastric tube). - Late (serum sickness) reaction: Develops about 7 days after treatment. It usually responds to antihistamines and corticosteroids.

3.10. COMPLICATIONS OF SNAKE VENOM &MANAGEMENT:

Hypotension and shock are treated with ASV, plasma expanders and vasoconstrictors. Russell's viper bite results in acute pituitary, adrenal insufficiency & responds to hydrocortisone. Hemostatic disturbances respond well to ASV. ASV is given to neutralize procoagulant and toxins. FFP, cryoprecipitate, fresh whole blood are given to restore coagulability. Bitten limb nursed in most comfortable position, slightly elevated.

Prophylactic antibiotics like penicillin and metronidazole should be given. If wound is incised use broad spectrum antibiotics.

RENAL FAILURE is due to multi factorial causes. Early correction of shock & ASV is important to avoid ARF. Situations of oliguria where ARF not established, frusemide with fluid challenge or mannitol challenge can be tried. MC cause of ARF is ATN and has good prognosis. 10% of cases develop ACN & it is bad prognosis.

Indication for dialysis[36]:

Patient is taken up for dialysis when his general condition deteriorates due to hyperkalemia, pulmonary edema, severe acidosis and when the renal parameters are raised. In non-oliguric renal failure, the decision is done based on raising renal parameters. Hemodialysis[37] is done in patients with normal hemodynamic status. Those who are hemodynamically unstable, Peritoneal dialysis[39] is done. Patient with AKI[38] recovers in 3 weeks. If the patient does not recover think of Cortical Necrosis and Biopsy is medial. Prognosis of patients with renal failure is very good and they recover with appropriate treatment. Prognosis of patients with cortical necrosis is poor. They go in for Chronic Kidney Disease[23].

4. MATERIALS AND METHODS

Setting : The work was carried out in the Dept.of Internal Medicine department and IMCU of Thanjavur Medical College, Thanjavur.

Design of the study : Observational study

Period of the Study : Six months – March 2017 to August 2017

Sample size : 50 cases (25cases and 25 controls)

Ethical committee approval : The present study was approved by the Institutional Ethical committee.

INCLUSION CRITERIA:

Patients with snake bite , developing Acute Kidney Injury.

EXCLUSION CRITERIA:

1) Known Hypertensive and on treatment.

2) Known Diabetic and on treatment

3) Chronic history of NSAID intake

4) Past history of renal disease.

5) Previous Ultrasonogram evidence of Chronic Kidney disease[20].

Consent:

The study group thus identified by the above criteria (inclusion and exclusion criteria) were first instructed about the nature of the study. Willing participants were taken up after getting a written informed consent from them.

Study Subjects and Controls:

Fifty cases with history of snake bite patients who got admitted in the Dept of Internal medicine of Thanjavur Medical college for the period of six months from March 2017 to August 2017 formed the study group. Out of these 25 patients were kept as controls and 25 patients kept as cases and they were assessed on who progressed to AKI[(24)] .

Details of study subjects:

All the cases were subjected to careful history taking and physical examination and biochemical parameters were done on the day of presentation .

CLINICAL EXAMINATION:

A thorough physical examination was done tolook for local and systemic features of envenomation.

EVIDENCE FOR REGIONAL ENVENOMATION:

Site of snake bite is examined for presence of fang marks, cellulitis,

bleeding from site of bite, local necrosis, blistering, gangrene, regional lymphnode enlargement and evidence for compartment syndrome.All Vital signs looked for.

EVIDENCE FOR SYSTEMIC ENVENOMATION:

Features of bleeding manifestations – gum bleeding, epistaxis, ecchymosis ;Features of NeuroparalysisAzotemia / Uremic symptoms.

INVESTIGATIONS:

1.blood urea

2.serum creatinine

3.urine albumin

4.platelet count[(2)]

Patients underwent physical examination daily. Pulse rate, Blood pressure,Urine output, Respiratory rate and features of envenomation were monitored daily. Blood specimen was taken everyday till discharge or death to measure sodium,potassium, urea, creatinine, bleeding time, clotting time, platelets and for patients undergoing dialysis, pre-dialysis and post-dialysis Urea and Creatinine measured for each cycle.

TREATMENT GIVEN:

1. Injection Tetanus Toxoid 0.5ml subcutaneous on admission.

2. Cleaning of the wound and area with soap and water.

3. IV line secured for fluids and ASV.

4. Specific treatment Inj ASV IV bolus and followed up doses depending upon the class of envenomation and biochemical parameters. Bite to ASV time noted.

5. Repeated doses of ASV based on signs of envenomation and biochemical parameters.

6. Maintenance of fluid volume, blood pressure.

7. Drugs Ampicillin, cefotaxime, metronidazole given in regular dose and dose adjustment has done depending upon renal status.

8. Observation.

9. Patient having evidence of Acute Kidney Injury[30] were identified.

10. Dialysis program based on volume overload, urine output status, clinical azotemia, uremic symptoms and renal biochemical parameters.

11. Repeated PD/HD depending upon the renal improvement.

5. STATISTICAL ANALYSIS.

a) The data were incorporated into statistical software and analyzed by Graph Pad prism version 5.

b) The data were expressed as mean with standard deviation for comparing the parameters between the groups.

c) The data were expressed as absolute numbers with percentage for describing the frequency of the parameters in case and control groups.

d) The unpaired ‘t’ test or Mann Whitney ‘U’ test was used to compare means between the case and control groups for normally distributed and non-normally distributed data, respectively.

e) Fisher’s exact test was used to find the statistical difference between the proportions.

f) $P<0.05$ was considered statistically significant difference.

6. RESULTS

6.1. AGE DISTRIBUTION OF THE STUDY SUBJECTS:

In our study of 50 patients, the total number of patients included under cases and controls were 25 each. The cases were the subjects who developed the elevated renal parameters after snake bite and controls were the subjects with normal renal parameters after snake bite injury.

The distribution of frequency of age in years was divided into six groups, namely, less than 20 years, 20 to 30 years, 31 to 40 years, 41 to 50 years, 51 to 60 years and > 60 years in cases and control groups. The absolute numbers with percentages of age in years between cases and controls based on category is represented in table 1.

In case group, the majority of the patients are of 41 to 50 years (n= 10, 40%), followed by < 20 years category (n=4, 16%) and the age category of 20-30 has least frequency (n=2, 8%).

In controls, the majority of the patients belong to the 31-40 years group (n=8, 32%) and 50 – 60 year group (n=8, 32%) and the age category of < 20 years and > 60 years have no subjects.

The overall mean age of the control group is 41.5 years with standard deviation of 12.1 years and in the case groups the mean age is 41.9 years with standard deviation of 16.3 years. The mean of both the age groups were compared by unpaired ‘t’ test and the p value obtained was 0.92. Hence, both the groups are similar in respect to age in years.

When overall the age distribution was considered without dividing into groups, with the sample of 50 subjects, most of the patients admitted with snake bite in our study falls under 41 to 50 years of group (n=13, 26%) followed by 31 to 40 and 51 -60 years group (n=11 ,22%). The age group of > 60 years has least

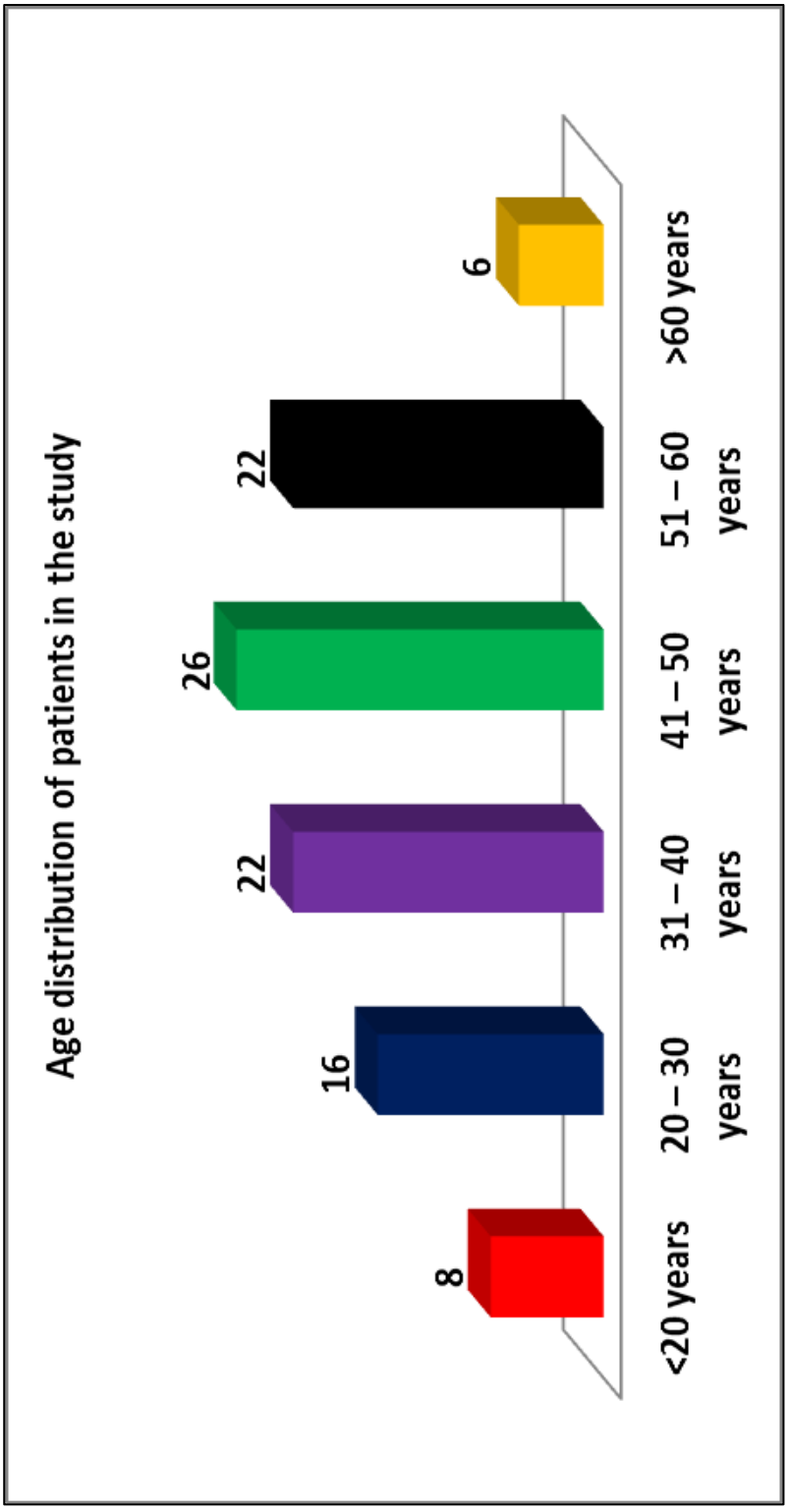
frequency distribution (n=3, 6%). The frequency distribution of overall age in years is represented in figure1.

Table 1: Frequency distribution of age of patients in the study subjects.

S.No	Age category in years	Cases (n=25)		Controls (n=25)	
		n	%	N	%
1	<20 years	4	16	0	0
2	20 – 30 years	2	8	6	24
3	31 – 40 years	3	12	8	32
4	41 – 50 years	10	40	3	12
5	51 – 60 years	3	12	8	32
6	>60 years	3	12	0	0
	Mean age with SD	**41.9 (16.3)**		**41.5 (12.1)**	

Foot note: The data are expressed as mean with standard deviation. The total n in the study sample is 50. The mean age between the groups are compared by unpaired ‘t’ test and the p value is 0.92 (Not significant).

Figure 1: Frequency distribution of age of patients in the study subjects (Overall).



6.2. GENDER DISTRIBUTION OF SUBJECTS IN THE STUDY.

The proportions of gender based on group in our study were shown in table 2. In the case group of 25 subjects, the male subjects were 76 % (n = 19) and the female subjects were 24 % (n=6). The proportion of male subjects was numerically higher than the female subjects in the case group.

Similarly, in control groups of 25 subjects, the male subjects were 68 % (n=17) and the female subjects were 32 % (n=8). The proportions of male subjects was numerically higher than the female subjects in the control group

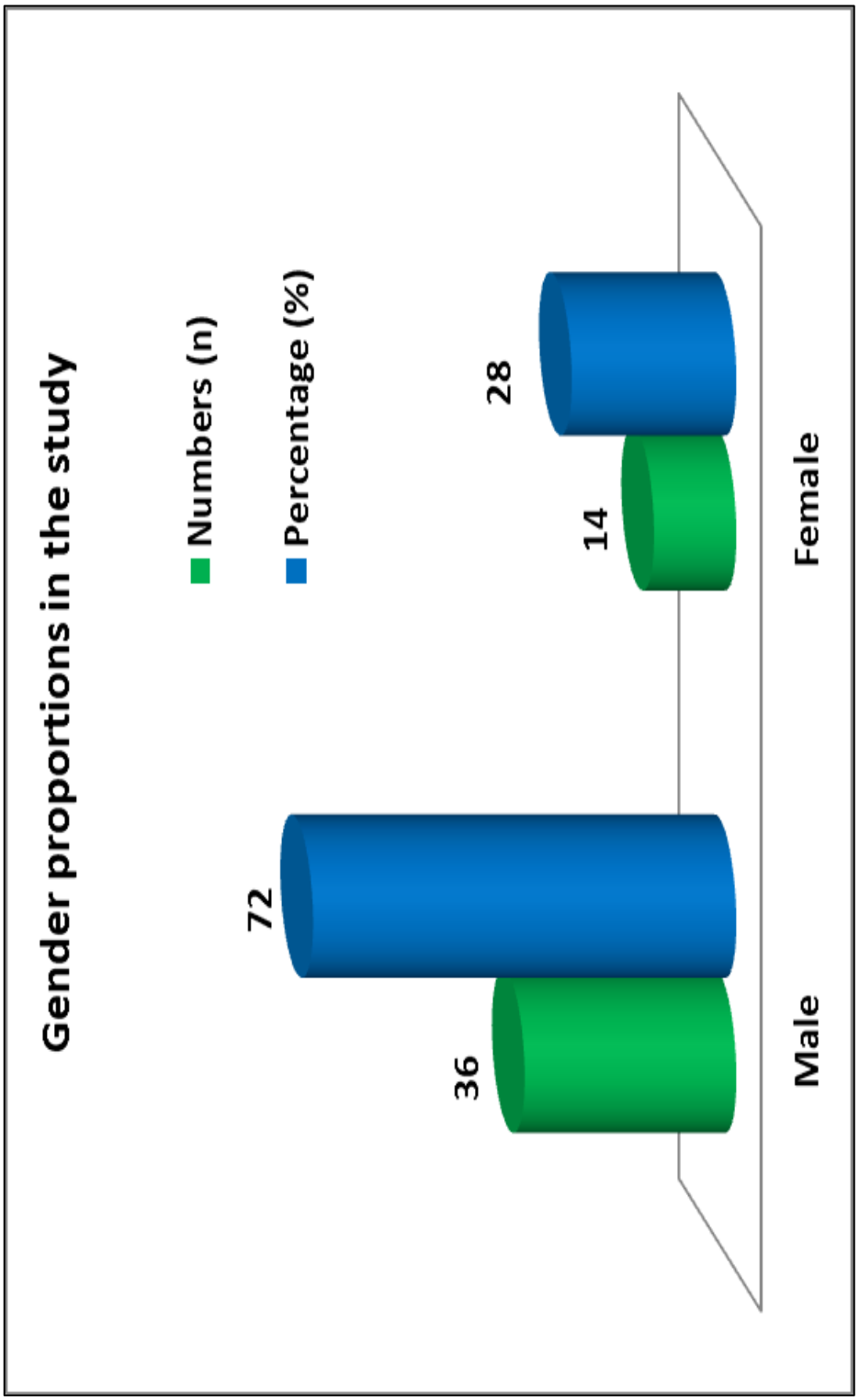
When all these proportions are compared between the groups based on gender by using Fisher's Exact test, the p value obtained was 0.87 (Not significant). Hence the gender proportions are equally distributed between the case and control group.

When the overall sample of 50 subjects was analyzed without dividing into groups, the male subjects were 72% (n=36) and the female subjects were 28% (n=14). Hence, in total, the male subjects were numerically higher than the female subjects in our study i.e the male subjects was admitted with higher frequency of snake bite than the female subjects in our study. This is represented in Figure2.

Table 2: Gender distribution of subjects in the study. (n=50)

S.No	Parameter	Cases (n=25)		Controls (n=25)	
		n	%	n	%
1	Male	19	76	17	68
2	Female	6	24	8	32

Figure 2: Proportion of gender distribution in the study (overall) n=50



6.3. TYPE OF SNAKES IN THE STUDY

In our study of 50 subjects, the unknown snake bite accounts for 24 % (n=12.) Amongst the known snake bite, the snake bite by Russell's Viper was the one with highest frequency (n=18, 36%).

This is followed by common krait snake bite (n=9, 18%) and Saw scaled Viper bite poisoning (n=7, 14%). In our study, the cobra bite was the one with least frequency of 8% (n=4).

This data are represented in table 3 and in figure 3.

Table 3: Frequency distribution of type of snake in the study population.

S.No	Type of snakes	Number (n)	Percentage (%)
1	Unknown	12	24
2	Russell's viper	18	36
3	Krait	9	18
4	Saw scaled Viper	7	14
5	Cobra	4	8

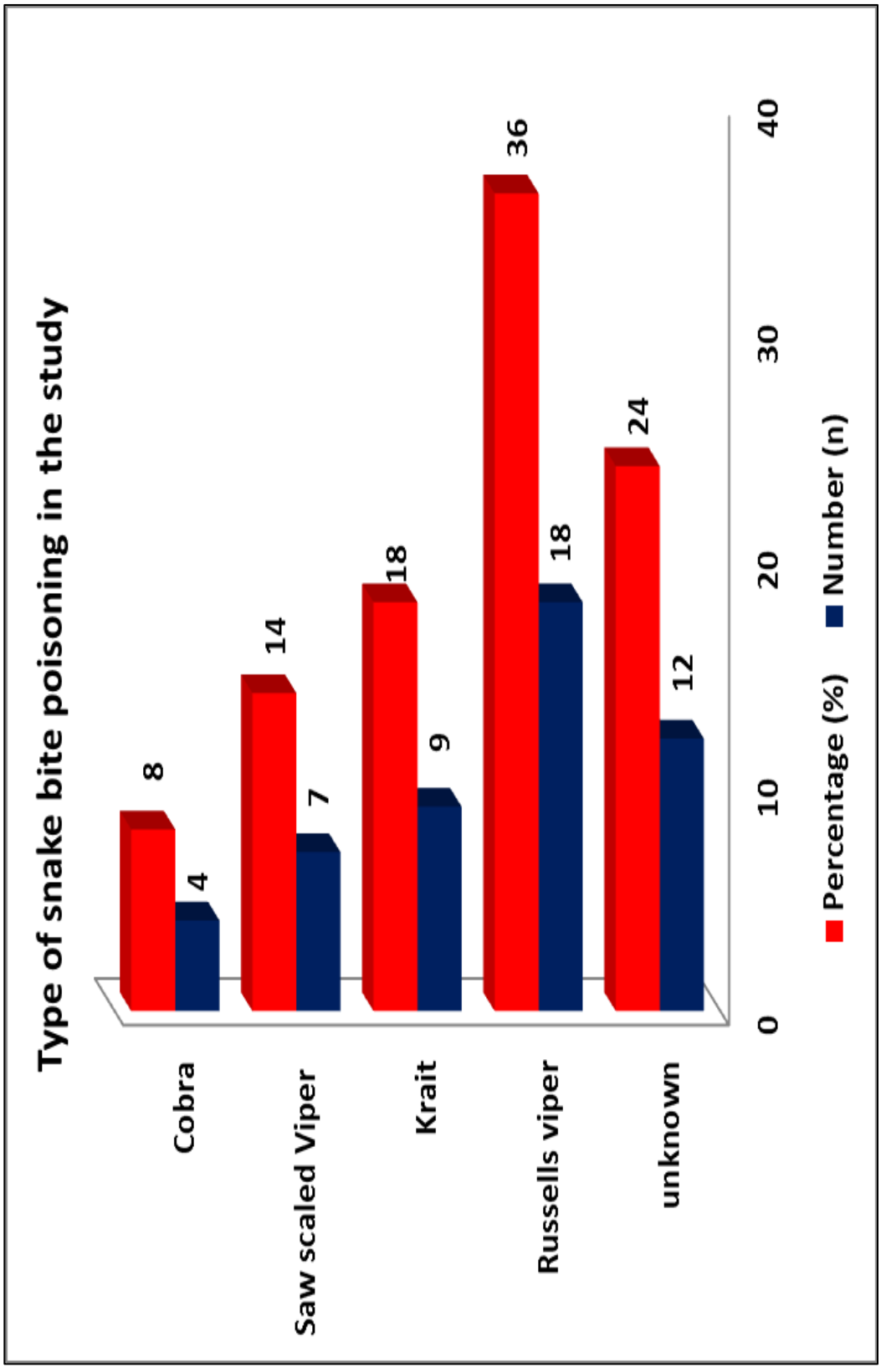


Figure 3: Frequency distribution of type of snake bite poisoning in the study population

6.4 OUTCOME OF THE PATIENTS IN THE STUDY SUBJECTS

The outcome of the patients in both control and case group of our study after snake bite is summarized in table 4. Out of 25 subjects in the control group, 84% (n=21) of patients were managed conservatively. The remaining 16% (n=4) of subjects in the control group underwent for dialysis[31]. In the 16% of subjects who underwent dialysis, 12% (n=3) underwent hemodialysis and 4% (n=1) has undergone for peritoneal dialysis.

In case group with the sample of 25 subjects, 12% (n=3) were expired during the study period. In the remaining patients, 32% (n=8) were managed conservatively and 56% (n=14) were needed dialysis. In the patients who underwent dialysis in cases group, numerically hemodialysis (n=9, 36%) is higher than the patients who underwent peritoneal dialysis (n=5, 20%).

The outcome of the patients in snake bite without considering the group is presented in figure 4. In a sample of 50 subjects, overall, majority of patients were managed by conservative treatment (n=29, 58%). The mortality is 6% (n=3) and all the patients who died belong to the case group. No mortality was observed in the control group. On a whole, the proportions of patients who underwent hemodialysis (n=12, 24%) is numerically higher than the patients who underwent peritoneal dialysis (n=6, 12%).

Table 4: Type of outcome (Management) given to the patients in the study population with snake bites in cases and controls groups.

S.No	Type of Management undergone by the patients	Cases (n=25)		Controls (n=25)	
		N	%	n	%
1	Hemodialysis	9	36	3	12
2	Peritoneal dialysis	5	20	1	4
3	Conservative Management	8	32	21	84
4	Expired	3	12	0	0

Data are expressed as absolute numbers with percentage. Total n=50 i.e 25/group.

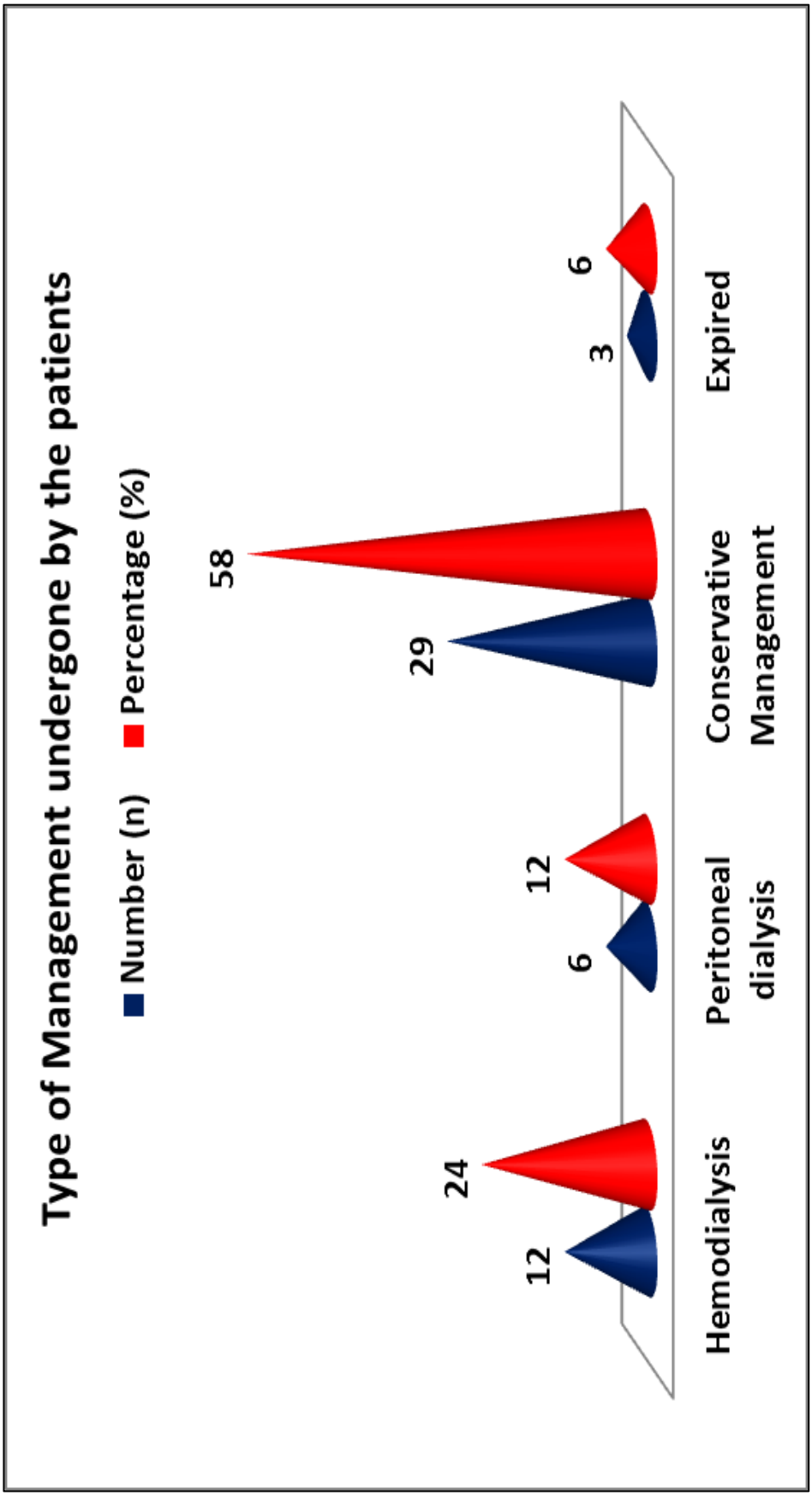


Figure 4: Frequency distribution of outcome (management) given to patients in the study (overall)

6.5 CLINICAL SIGNS OF SNAKE BITES IN THE STUDY SUBJECTS.

The major clinical signs such as cellulitis development and bleeding tendencies were assessed and reported in the table 5.

In the control group of 25 subjects, the proportions of patients who developed cellulitis is 64 % (n=16) and who did not develop cellulitis was 36% (n=9). In case group, 84% (n=21) has developed cellulitis and only 16% has no cellulitis. Hence, the proportion of patients who developed cellulitis in the snake bite is higher than those who did not develop in both the case and control groups.

When these proportions are compared between the case and control groups by using Fisher's Exact test, the p value obtained was 0.19 (Not significant). Hence, there is no statistical significant difference between the case and control group when the proportions of development and not-development of cellulitis were considered.

Similarly, in control group with a sample of 25 subjects, 40% (n=10) of the patients developed bleeding manifestation after snake bite and 60% (n=15) of subjects did not develop bleeding manifestations. When the proportions of bleeding manifestations in case group of 25 subjects were considered, it has been observed that the 44% (n=11) developed bleeding manifestations and 56% (n=14) did not develop bleeding manifestation.

When these proportions are compared between the case and control groups by using Fisher's Exact test, the p value obtained was 0.99 (Not significant). Hence, there is no statistical significant difference between the case and control group when the proportions of development and not-development of bleeding tendencies were considered. The results are summarize in table 5.

Table 5: Comparison of proportions of cellulitis and clinical bleeding development between cases and controls in the snake bite.

Data are expressed as absolute numbers with percentage.

S.No	Parameter		Cases (n=25)		Controls (n=25)		P Value
			n	%	N	%	
1	Cellulitis	Present	21	84	16	64	0.19 (NS)
		Absent	4	16	9	36	
2	Clinical Bleeding	Present	11	44	10	40	0.99 (NS)
		Absent	14	56	15	60	

6.6 EFFECT OF SNAKE BITE IN THE BIOCHEMICAL PARAMETERS IN THE STUDY.

The biochemical parameters such as Blood urea (mg/dl), Serum creatinine (mg/dl), Platelet count[3] (lakhs/cc) and urine albuminuria[22] were analyzed between the case and control groups. The results are expressed in table 6 and table 7.

In controls with the sample of 25 subjects, the mean blood urea was 29.4 mg/dl with the standard deviation of 5.61 mg/dl. In cases group with the sample of 25 subjects, the mean blood urea was 77.8 mg/dl with the standard deviation of 10.8 mg/dl. Hence, the mean blood urea value of case groups is numerically higher than the mean blood urea value of control group (77.8 mg/dl Vs 29.4 mg/dl).

To obtain the statistically significant difference between the means, unpaired 't' test was used to test the null hypothesis (77.8 ± 10.8 Vs 29.4 ± 5.61). The p value obtained was <0.0001 which is considered extremely significant. Hence, the mean blood urea values in the case groups are statistically higher than the mean blood urea value of control groups.

Table 6: Comparison of different biochemical parameters between cases and controls

S.No	Biochemical parameters	Cases (n=25)		Controls (n=25)		P Value
		Mean	SD	Mean	SD	
1	Blood Urea (Mg/dl)	77.8	10.8	29.4	5.61	<0.0001*
2	Serum Creatinine (mg/dl)	2.8	1.03	0.86	0.14	<0.0001*
3	Platelet count (Lakhs/cc)	1.12	0.38	1.7	0.37	<0.0001*

Data are expressed as mean with standard deviation. Unpaired ‘t’ test was used to test the level of significance. * indicates $p<0.05$ and considered statistically significant.

Similarly in controls with the sample of 25 subjects, the mean serum creatinine was 0.86 mg/dl with the standard deviation of 0.14 mg/dl. In cases group with the sample of 25 subjects, the mean serum creatinine was 2.8 mg/dl with the standard deviation of 1.03 mg/dl. Hence, the mean serum creatinine value of case groups is numerically higher than the mean serum creatinine value of control group (2.8 mg/dl Vs 0.86 mg/dl).

To obtain the statistically significant difference between the means, unpaired ‘t’ test was used to test the null hypothesis (2.8 ± 1.03 Vs 0.86 ± 0.14). The p value obtained was <0.0001 which is considered extremely significant. Hence, the mean serum creatinine values in the case groups are statistically higher than the mean serum creatinine value of control groups.

In the same way, the platelet count between the groups was compared. In controls with the sample of 25 subjects, the mean platelet count was 1.7 Lakhs/cc with the standard deviation of 0.37 Lakhs/cc. In cases group with the sample of 25 subjects, the mean platelet count was 1.12 Lakhs/cc with the standard deviation of 0.38 Lakhs/cc. Hence, the mean platelet count value of case groups is numerically lower than the mean platelet count value of control group (1.12 mg/dl Vs 1.7 mg/dl).

To obtain the statistically significant difference between the means, unpaired ‘t’ test was used to test the null hypothesis (1.12 ± 0.38 Vs 1.7 ± 0.37). The p value obtained was <0.0001 which is considered extremely significant. Hence, the mean platelet count values in the case groups are statistically lower than the mean platelet count value of control groups.

The frequency distribution of urine albuminuria between cases and control groups are summarized in table 7. The four categories of albuminuria are Nil, Trace, 1 plus and 2 plus.

In control group with the 25 subjects, the highest frequency was observed in the ‘trace category’ (n=10, 40%), followed by Nil urine albumin category (n=9, 36%) and the 1 plus urine albumin category (n=6, 24%). No patients had urine albumin 2+ category in the control group.

In case group with the 25 subjects, the highest frequency was observed in the ‘ urine albumin plus 2 category’ (n=10, 40%), followed by urine albumin 1plus category (n=8, 32%) and the urine albumin trace category (n=6, 24%). Only one

patient was under urine albumin nil category in the control group. Hence, on a whole, the proportion of the urine albuminuria is numerically higher in the case group than the control group patients.

Table 7: Comparison of frequency distribution of urine albuminuria between case and control groups

S.No	Type of urine albuminuria	Cases (n=25)		Controls (n=25)	
		n	%	n	%
1	Nil	1	4	9	36
2	Trace	6	24	10	40
3	1 plus	8	32	6	24
4	2 plus	10	40	0	0

Data are expressed as absolute numbers with percentages.

6.7. EFFECTS OF SNAKE BITE ON ALBUMINURIA AND AS AN EARLY PREDICTOR OF ACUTE KIDNEY INJURY.

In both cases and control groups of our study, for the purpose of description, the urine albumin Nil and Trace category were clubbed together as "Albuminuria Absent'. The remaining groups, albumin 1 Plus and albumin 2 plus were clubbed together as 'Albuminuria Present' group.

In the control group of 25 subjects, the proportion of patients who has albuminuria was 24% (n=6) and who did not have albuminuria was 76%

(n=19). The proportion of the patients with albuminuria present is numerically lower than the proportion of patients with albuminuria absent.

In case group of 25 subjects, the proportions of patients who has albuminuria was 72% (n=18) and who did not have albuminuria was 28% (n=7). The proportion of the patients with albuminuria present is numerically higher than the proportion of patients with albuminuria absent.

To test the statistical difference between these proportions, Fisher's Exact test was used and the p value obtained was 0.0015 (statistically significant). The relative risk obtained is 2.78 with 95% confidence interval of 1.41 to 5.4. The data are summarized in the table 8.

Table 8: Comparison between the cases and controls in regards to the development of albuminuria .

S.No	Parameter		Cases (n=25)		Controls (n=25)		P Value	Relative risk (95% CI)
			n	%	n	%		
1	Albuminuria	Present	18	72	6	24	0.0015*	2.78 (1.41 to 5.4)
		Absent	7	28	19	76		

The frequencies of albuminuria – NIL and traces are clubbed together for albuminuria absent group and 1+ & 2+ are combined for albuminuria present category. Fisher's Exact test was used to test the level of significance.

6.8. EFFECTS OF SNAKE BITE ON PLATELET COUNT AND AS AN EARLY PREDICTOR OF ACUTE KIDNEY INJURY.

In both cases and control groups of our study, for the purpose of description, the patients with platelet count less than 1.5 lakhs/cc was taken as

'Thrombocytopenia Present' and the patients with platelet count above 1.5 lakhs/cc was taken as 'Thrombocytopenia[22] absent' group.

In the control group of 25 subjects, the proportion of patients who has thrombocytopenia was 28% (n=7) and who did not have thrombocytopenia was 72% (n=18). The proportion of the patients with thrombocytopenia present is numerically lower than the proportion of patients with thrombocytopenia absent (28% Vs 72%).

In case group of 25 subjects, the proportions of patients who has thrombocytopenia was 76% (n=19) and who did not have thrombocytopenia was 24% (n=6). The proportion of the patients with thrombocytopenia present is numerically higher than the proportion of patients with thrombocytopenia absent.

To test the statistical difference between these proportions, Fisher's Exact test was used and the p value obtained was 0.0016 (statistically significant). The relative risk obtained is 2.92 with 95% confidence interval of 1.4 to 6. The data are summarized in the table 9.

Table 9: Comparison between the cases and controls in regards to the thrombocytopenia.

S. No	Parameter		Cases (n=25)		Controls (n=25)		P Value	Relative risk (95% CI)
			n	%	n	%		
1	Thrombocytopenia	Present	19	76	7	28	0.0016*	2.92 (1.4 to 6)
		Absent	6	24	18	72		

7. DISCUSSION:

Our study aimed to determine the early prediction of acute kidney injury in the patients with snake bite by urine albuminuria and thrombocytopenia. The control groups are the patients with normal renal parameters after snake bite and the cases were the patients with elevated renal parameters after the snake bite.

In our study, it was found that

1. The mean platelet count was significantly lower in the patients with elevated renal parameters than the patients with normal renal parameters after the snake bite.
2. The proportions of patients with albuminuria are higher in the case groups than the control groups.
3. The proportions of patients with thrombocytopenia are higher in the case groups than the control group.
4. The age of the patients in both the groups are equally distributed between the case and control groups.
5. The gender proportion in both the case and control groups are equally distributed
6. Mortality due to snake bite is 6%
7. The common type of snake bite happened is Russell's Viper
8. Majority of the patients who developed acute kidney injury were treated with conservative management.

9. Clinical presentation like cellulitis and bleeding tendencies are equally distributed in both the groups.

The age group of the patients with snake bite in our study with highest frequency is between 41 to 50 years and mean age in both case and controls were 41.9 and 41.5 years with no significant differences.

Others studies conducted by Chugh KS[62] et al , Pinho F M[63] et al , Naqvi R [64]et al and Mukhopadhyay P[65] et al found that the mean age in snake bite poisoning is varying from 24 years to 43 years. Our study also has the mean age of patients with snake bite fall under the similar category to other studies.

In both case and control groups, the males have the higher frequencies of snake bite poisoning than the female. This could be due to the fact that, being a male gender, the probability of going to work outside the home is higher than the female and hence the chances of accidental bite from the snake is higher in both the groups than the females.

Other studies conducted by Pinho F M[63] et al , Naqvi R[64] et al , Mukhopadhyay P[65] et al , Athappan G[66] et al and Krishnamurthy S[67] et al found out the similar inference that the snake bite is higher in males than the females. The ratio of male to female in snake bite ranges from 4:1 in study

conducted by Ahuja [69]and Singh et al to 7:3 in study conducted by Bhat [69] et al. Our study is also in concordance with the other studies in this aspect.

Moreover, in our study both the age and gender were equally distributed between the groups. This rules out the baseline differences between the groups which can significantly affect the outcome, in our study the outcome being the development of acute kidney injury. It is well known fact that the renal function will be decreased with increasing age and hence age difference between the groups can make the interpretation of statistical differences between the group questionable. However, in our study, both the age and gender were equally distributed between the groups.

The most common type of snake bite seen in our study is due to Russell's viper. Russell's viper along with common krait, cobra and saw scaled Viper constitutes the major four Snakes which are responsible for almost all of the snake bites in India. This is in concordance with the study conducted by Warell DA et al ,Swaroop S et al , N. Suchitra [70]et al and G. Ali et al.

The mortality rate observed in our study due to snake bite poisoning was 6%. The mortality due to snake bite poisoning in India is around 40,000 cases per year in 1963 which has come down to less than 2000 per year in 2010 as indicated by Shubhanker M[72] et al . This fact is mainly due to the easy and frequent availability of anti snake venom in the various tertiary care hospitals.

Similar studies which aimed to estimate the mortality rate due to snake bite poisoning in India such as Viramani [73]SK et al , Bawaskar HS [74]et al , Brunda G[75] et al and Majumder D[76] et al reported that the mortality rate as higher values ranging from 40% to 80%. However in our study we observed only 6% mortality rate. This could be due to two facts.

First of all, our study was conducted in a tertiary care hospital which has surplus access to the anti-snake venom and the complications developed were managed effectively with life support care. Second, on retrospective analysis, it was found that majority of the cases included in the study was residing within 50 kilometers radius from the hospital. Hence with advance treatment and easy access to the hospital could make the mortality rate low in our study similar to Kalantri S[77] et al and Kulkarni [78]et al study (mortality 2.6 and 5.2% respectively).

Acute kidney injury is the most dreaded complication which can develop in the snake bite, especially with hemotoxic snake bite like Viper bites. In our study conducted in 50 subjects with acute kidney injury due to snake bite, the majority of the patients were managed conservatively (58%) and 36% required dialysis.

The proportion of patients underwent dialysis is higher in the case groups than the control groups (56% Vs 16%). Studies conducted by Pinho F M[63] et al , Athappan G [66]et al , and Kalana M et al have reported that the Acute Kidney

injury is the one of the common complications which can develop in the hemotoxic snake bite. In our study, the commonest snake bite poisoning noted was Russell's Viper. Hence the higher proportions of hemodialysis required in our study could be partly explained by the type of snake poisoning: Russell's Viper in our case.

Cellulitis and bleeding tendencies are the more common complication observed in the snake bite besides Acute Kidney Injury. In the study conducted by Athappan G[66] et al the cellulitis was observed in higher frequencies. In our study, overall (50 subjects), 74% subjects developed cellulitis while 26% patient did not develop cellulitis. This proportion is similar to study conducted by Athappan G[66] et al.

Similarly, in the studies conducted by N. Suchitra[70] et al and G. Ali et al the bleeding tendencies observed was significantly associated with the development of Acute kidney injury. In our study, overall, 42% developed clinical bleeding while 58% did not develop the clinical bleeding manifestations. This proportion is slightly higher than the frequency observed in study conducted by Athappan G[66] et al (22.7%). However, the bleeding tendencies noted in our study is comparable with study conducted by N. Suchitra [70]et al and G. Ali et al. These varying results in proportion of bleeding tendencies noted in the study can be relatively explained by the fact that the bleeding tendency depends on many factors. Factors like type of snake

envenomation, amount of toxin injected and presence of other co-morbidity contributes in large.

The mean platelet count observed in the control group (patients with normal renal parameters in snake bite poisoning) was 1.7 lakhs/cc with the standard deviation of 0.37. However, the mean platelet count noted in the case group (patients who developed elevated renal parameters after snake bite) was 1.12 lakhs/cc with standard deviation of 0.38. This indicates that the mean platelet count in the case group falls under thrombocytopenia category. Moreover we also found the statistical significant difference between mean platelet count between the cases and controls (1.7±0.37 in control Vs 1.12 ± 0.38 in case). The patients with elevated renal parameters after snake bite developed thrombocytopenia and their platelet count was significantly lower than the patients with normal renal parameters.

Severe blood loss can be caused by the bleeding tendencies in the snake bite. Pinho F M[63] et al , Athappan G[66] et al N. Suchitra[70] et al, G. Ali et al and Sharma et al have found that the bleeding tendencies in the snake bite as the good associative factor in occurrence of Acute Kidney injury. Our study is also in concordance with these facts.

In our study, when the proportion of development of thrombocytopenia was compared with those who did not develop in case and control group, the relative risk obtained was 2.92 (95% confidence interval of 1.4 to 6; p value of

0.00016). Hence it could be noted that the patients who developed thrombocytopenia after snake bite will have 2.92 times higher risk of having acute kidney injury.

Many predictors of acute kidney injury like bite to hospital time, low systolic blood pressure on presentation, bleeding time and albuminuria were reported in various studies. Paul [81]et al has found that hematuria and albuminuria was associated with development of acute kidney injury.

In our study, in case groups, 72% developed albuminuria and only 24% developed albuminuria in control groups. When the proportions are compared between the groups, we found significant higher proportion of albuminuria in case groups. The relative risk obtained was 2.78 (95% confidence interval of 1.41 to 5.4). Hence, the risk of developing acute kidney injury was 2.78 times higher in the patients with albuminuria than those without albuminuria. This finding was in concordance with the study conducted by Mrudul V[82] et al . Hence from the above results it could be inferred that the albuminuria and thrombocytopenia are strongly associated with development of acute kidney injury.

The major limitations in our study was that we did not considered other factors that could possibly affect the development of acute kidney injury like time to hospital, dose of ASV administered and development of hypotension. In future studies, multivariate analysis considering all the possible factors affecting

the outcome of patients with snake bite with same study design would provide further information. Nevertheless our study gives a direct evidence(based on relative risk) that the albuminuria and thrombocytopenia in the setting of snake bite could predict the need for dialysis at an early stage .

8. CONCLUSION:

In patients with snake bite,

a. Albuminuria and thrombocytopenia are associated with development of Acute kidney injury
b. Presence of thrombocytopenia can predict the occurrence of Acute Kidney Injury at the earlier stage.
c. Presence of albuminuria can predict the occurrence of Acute kidney Injury at the earlier stage.

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PROFORMA

"A STUDY ON THROMBOCYTOPENIA AND ALBUMINURIA AS EARLY PREDICTORS OF AKI IN SNAKE BITE"

PARTICULARS OF THE PARTICIPANT :

Name: Age: Sex: M/F Diet: V/NV
Address: Occupation:

PRESENTING COMPLAINT:

H/O SNAKE BITE YES/NO

DURATION BETWEEN BITE TIME AND HOSPITAL ADMISSION:

NATURE OF SNAKE:

SPECIFIC COMPLAINT:

PAST HISTORY :

□ DM □ HT □ Renal disorders

GENERAL EXAMINATION :

Blood Pressure:
Pulse Rate:
Pedal edema:

SYSTEMIC EXAMINATION :

CVS : R/S :

ABDOMEN : CNS :

INVESTIGATIONS :

BloodUrea : Serum Creatinine :

Urine - Albumin : Platelet Count:

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR .J.SUDHAKARAN ,** Post graduate in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of participant

INFORMATION SHEET

We are conducting a Observational study on "**A STUDY ON THROMBOCYTOPENIA AND ALBUMINURIA AS EARLY PREDICTORS OF AKI IN SNAKE BITE" (MARCH 2017 -AUGUST 2017)**in the Dept. of Internal Medicine and IMCU, Thanjavur Medical College & Hospital,Thanjavur – 613004.

- At the time of announcing the results and suggestions, name and identity of the patients will be confidential.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator **Signature of participant**

Date:

Master Chart Page 1

S. No	name	Age	sex	blood urea g/dl1	sr creatinine mg/dl	Platelet count (in lakhs/cc)	urine albu min	Presence of clinical bleeding	Type of snake	Presence of cellulitis	Dialysis type/ outcome	GROUP
1	murugan	33	M	26	0.85	1.25	1+	NO	RUSSELS VIPER	YES	CONS	CONTROL
2	govinda raj	55	M	34	0.6	2.2	trace	YES	KRAIT	NO	CONS	CONTROL
3	muthu	38	M	39	1.1	2	nil	NO	RUSSELS VIPER	YES	CONS	CONTROL
4	jayaraman	50	M	29	1.0	2.46	1+	NO	SAWSCALED VIPER	YES	CONS	CONTROL
5	jayaraman	55	M	33	0.75	0.9	nil	YES	UNKNOWN	NO	CONS	CONTROL
6	neelavathy	35	F	36	0.8	1.5	trace	NO	SAWSCALED VIPER	YES	CONS	CONTROL
7	anthonysamy	60	M	27	0.9	1.8	trace	YES	UNKNOWN	NO	CONS	CONTROL
8	kaliyarajan	30	M	92	4.0	1.89	nil	NO	RUSSELS VIPER	YES	HD	CONTROL
9	muniyan	55	M	36	0.8	1.24	nil	NO	UNKNOWN	YES	CONS	CONTROL
10	prashanth	24	M	31	0.7	2.02	1+	YES	SAWSCALED VIPER	YES	CONS	CONTROL
11	shanmugam	45	M	27	0.6	1.17	trace	YES	COBRA	YES	CONS	CONTROL
12	suguna	31	F	23	0.8	1.8	1+	YES	UNKNOWN	YES	CONS	CONTROL
13	kamaraj	40	M	58	2.8	1.67	trace	NO	RUSSELS VIPER	YES	PD	CONTROL
14	gopi	35	M	35	0.9	1.8	nil	NO	RUSSELS VIPER	YES	CONS	CONTROL
15	govindha samy	55	M	34	0.9	2	trace	NO	KRAIT	YES	CONS	CONTROL
16	muniyamal	30	F	26	1.0	1.28	1+	NO	RUSSELS VIPER	YES	CONS	CONTROL
17	lalitha	35	F	82	5.6	1.89	nil	NO	UNKNOWN	NO	HD	CONTROL

Master Chart Page 2

S. No	name	age	sex	blood urea g/dl1	sr creatinine mg/dl	Platelet count (in lakhs/cc)	urine albu min	Presence of clinical bleeding	Type of snake	Presence of cellulitis	Dialysis type/outco me	GROUP
18	kanagavalli	21	F	26	0.6	2.1	nil	NO	SAWSCALED VIPER	NO	CONS	CONTROL
19	raja	45	M	33	0.8	1.91	nil	YES	UNKNOWN	NO	CONS	CONTROL
20	chellammal	55	F	37	0.8	1.14	trace	NO	KRAIT	NO	CONS	CONTROL
21	jayam	55	F	33	0.9	1.47	trace	NO	RUSSELS VIPER	YES	CONS	CONTROL
22	shanmugam	30	M	96	6.8	1.7	trace	NO	RUSSELS VIPER	YES	HD	CONTROL
23	rajesh	28	M	26	0.9	1.9	1+	YES	KRAIT	NO	CONS	CONTROL
24	subbaiya	60	M	27	0.9	1.72	nil	YES	SAWSCALED VIPER	NO	CONS	CONTROL
25	jayanthi	38	F	22	0.8	1.8	trace	YES	UNKNOWN	YES	CONS	CONTROL
26	natarajan	46	M	60	1.6	1.3	nil	NO	KRAIT	YES	CONS	CASES
27	padmini	50	F	62	1.4	0.67	trace	NO	RUSSELS VIPER	YES	CONS	CASES
28	mahendran	44	M	56	4.2	1.8	trace	NO	COBRA	YES	EXPIRED	CASES
29	mohan	50	M	79	3.7	1.2	1+	NO	UNKNOWN	YES	CONS	CASES
30	vijaya kumari	44	F	60	3.1	0.75	1+	YES	KRAIT	YES	PD	CASES
31	selvarani	56	F	80	4.6	1.04	1+	YES	SAWSCALED VIPER	YES	HD	CASES
32	chinnappa	54	M	72	6.8	0.76	2+	YES	RUSSELS VIPER	YES	HD	CASES
33	solomon	40	M	85	2.6	1.7	trace	YES	RUSSELS VIPER	NO	PD	CASES
34	selvi	45	F	54	3.6	1.11	2+	YES	UNKNOWN	YES	CONS	CASES

Master Chart Page 3

S. No	name	age	sex	blood urea g/dl1	sr creatinine mg/dl	Platelet count (in lakhs/cc)	urine albumin	Presence of clinical bleeding	Type of snake	Presence of cellulitis	Dialysis type/Outcome	GROUP
35	kandan	65	M	72	3.7	1.2	1+	NO	SAWSCALED	YES	CONS	CASES
36	suresh	18	M	77	5.3	1.6	1+	NO	KRAIT	YES	HD	CASES
37	bharath pavith	18	M	60	1.4	0.87	1+	NO	RUSSELS VIPER	NO	CONS	CASES
38	pandian	42	M	79	6.7	0.96	2+	NO	COBRA	YES	HD	CASES
39	narayana swamy	70	M	89	6	1.76	trace	NO	UNKNOWN	YES	HD	CASES
40	elancheliyan	21	M	78	3.4	0.8	2+	YES	RUSSELSVIPER	YES	HD	CASES
41	sakthivel	17	M	80	1.4	1.7	trace	NO	KRAIT	NO	HD	CASES
42	laksmanan	12	M	58	1.8	0.96	2+	YES	RUSSELS VIPER	YES	CONS	CASES
43	tamil selvan	46	M	78	1.9	0.67	2+	NO	RUSSELS VIPER	NO	PD	CASES
44	gnanamary	47	F	89	4.1	0.91	2+	YES	COBRA	YES	HD	CASES
45	paramasivam	34	M	78	3.4	0.78	2+	YES	UNKNOWN	YES	EXPIRED	CASES
46	manavalan	68	M	90	3.6	0.73	trace	NO	RUSSELS VIPER	YES	EXPIRED	CASES
47	saroja	45	F	89	3.4	1.6	2+	YES	RUSSELS VIPER	YES	HD	CASES
48	haji ibram shah	58	M	58	3.1	1.08	1+	YES	KRAIT	YES	CONS	CASES
49	kumar	38	M	96	4.7	0.7	1+	NO	UNKNOWN	YES	PD	CASES
50	Madhankumar	21	M	78	1.9	1.36	2+	NO	RUSSELS VIPER	YES	PD	CASES