Dissertation on

"A STUDY TO CORRELATE ELEVATED CREATININE PHOSPHOKINASE WITH SNAKE BITE AND ACUTE KIDNEY INJURY"

Submitted in partial fulfillment of requirements of

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CHENNAI

2018

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled "A **STUDY TO CORRELATE ELEVATED CREATININE PHOSPHO KINASE WITH SNAKE BITE AND ACUTE KIDNEY INJURY"** is the bonafide work of **Dr. K. KIRTHIKA** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in **April 2018.**

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CERTIFICATE FROM THE GUIDE

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DECLARATION

I, Dr. K. KIRTHIKA declare that, I carried out this work on" **A STUDY TO CORRELATE ELEVATED CREATININE PHOSPHO KINASE WITH SNAKE BITE AND ACUTE KIDNEY INJURY''** at the Department of Medicine, Govt. Rajaji Hospital during the period **JANUARY 2016 TO MAY 2016**. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree or diploma to any other University, Board either in India or abroad.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of **M.D Degree General Medicine Branch- I**; examination to be held in **April 2018.**

Place : Madurai **Dr. K. KIRTHIKA**

Date :

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INTRODUCTION

“ India , similar to global incidence in estimation to have the highest snakebite mortality. WHO estimated the number of bites to be 83,000 with 11,000 deaths per annum. Much of the fatalities are due to the victims not reaching the primary care in time where treatment can be administered”.

“ Moreover people are not much informed about the occupational risks and the measures which will prevent snake bites. They continue to adopt harmful practices such as tourniquets ,or cutting and sucking , etc. Observations reveals that the primary care centres do not treat snakebite patients primarily due to lack of expertise and confidence”.

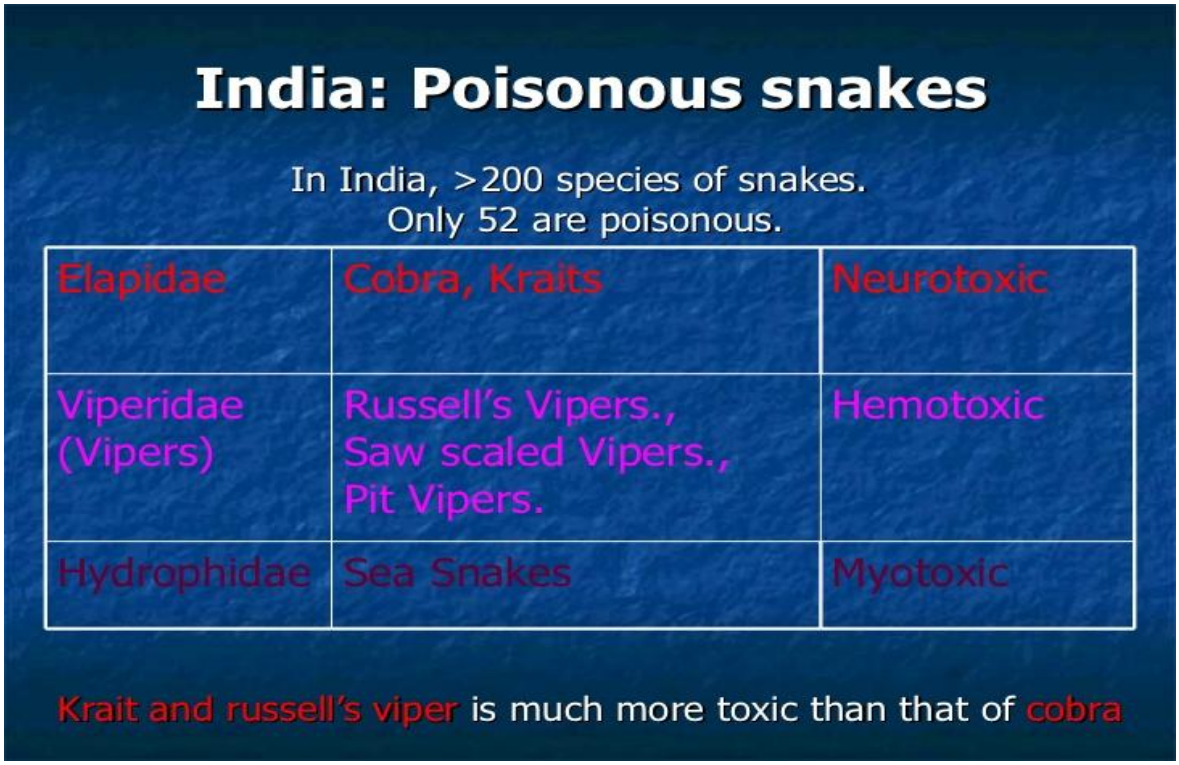
“But At the secondary and tertiary care level, more than 2 region specific protocols are followed for anti-snake venom (ASV) treatment”

“Snake is the most commonly used term for the “serpentes” family of reptiles .Out of which only about 20% of snakes are venomous and hence medically important”.

“Venomous snake has specialized venom synthesizing apparatus and fangs, favoring effective venom delivery. Venom producing snakes come from

family of Elapidae, Viperidae, Colubridae, and Atractaspididae. But most of the burden is caused by bites of vipers and elapids. Much commonly, vipers significantly causes coagulopathy, renal failure when compared with elapids which causes neurotoxicity".

RUSSELL'S VIPER



"It might be clear that in most parts of the South East Asia, they form an important emergency and reason for hospital admissions. This can result in either death or disability of most of the younger and working population, most commonly those involved in the farming or plantation works. The truer scale of mortality and even morbidity from snake-bites remain not to be certain because of not adequate reporting in most of the country".

"To remedy this situation, strong recommendations should be made as snake bite to be a notifiable disease in all countries of South East Asian regions".

"Much of Snake-bite is are seen in people who involve in occupations of farmers, plantation workers, herdsmen, fisherman, daily labourer and other producer. Therefore it is a medical problem that has an important implication for mainly nutrition and economy of the country where it occurs most commonly".

"The proposed recommendations are that of snake-bite should be notified and be recognized as much important occupational diseases of South East Asian region".

" Inspite of its importance, there have been very few clinical studies of snake-bite when compared to that of any other tropical diseases. Snakebite probably cause more deaths in the landscape region than do *amoebiasis.* But only about a small fraction of the research contribution in amoebiasis has been given to the snake-bite".

"Clinical Diagnosis of species of snakes which is responsible for bite will be important for ideal clinical treatment".

"If the bite has neurotoxic features with bulbar and respiratory involvement, anti snake venom only cannot be beleived upon to prevent rapid death due to asphyxiation. Neostigmine and ventilatiory support is necessary in such cases".

"in cases of AKI, Conservative management or rarely, hemodialysis is effective along with supportive treatment in victims of Russell's or , humped-nosed viper or sea snake-bites".

"But Fasciotomy will not be done in snake-bite cases unless and until coagulant abnormalities have been treated, or with features of intra compartmental features

is present or a high intra compartmental pressure should be confirmed by invasive/ direct measurement".

"There is a syndromic approach which should be developed for detecting species that may be responsible for snake-bite in different regions".

Syndrome 1

Local envenoming (swelling etc.) with bleeding/clotting disturbances = **Viperidae (all species)**

Syndrome 2

Local envenoming (swelling etc.) with bleeding/clotting disturbances, shock or acute kidney injury **= Russell's viper (hump-nosed pit viper in Sri Lanka and SW India)**

with conjunctival oedema (chemosis) and acute pituitary insufficiency **= Russell's viper, Myanmar**

with ptosis, external ophthalmoplegia, facial paralysis etc and dark brown urine **= Russell's viper, Sri Lanka and South India**

Syndrome 3

Local envenoming (swelling etc.) with paralysis **= cobra or king cobra**

Syndrome 4

Paralysis with minimal or no local envenoming

Bitten on land while sleeping on the ground **= krait**

Bitten in the sea, estuary and some freshwater lakes **= sea snake**

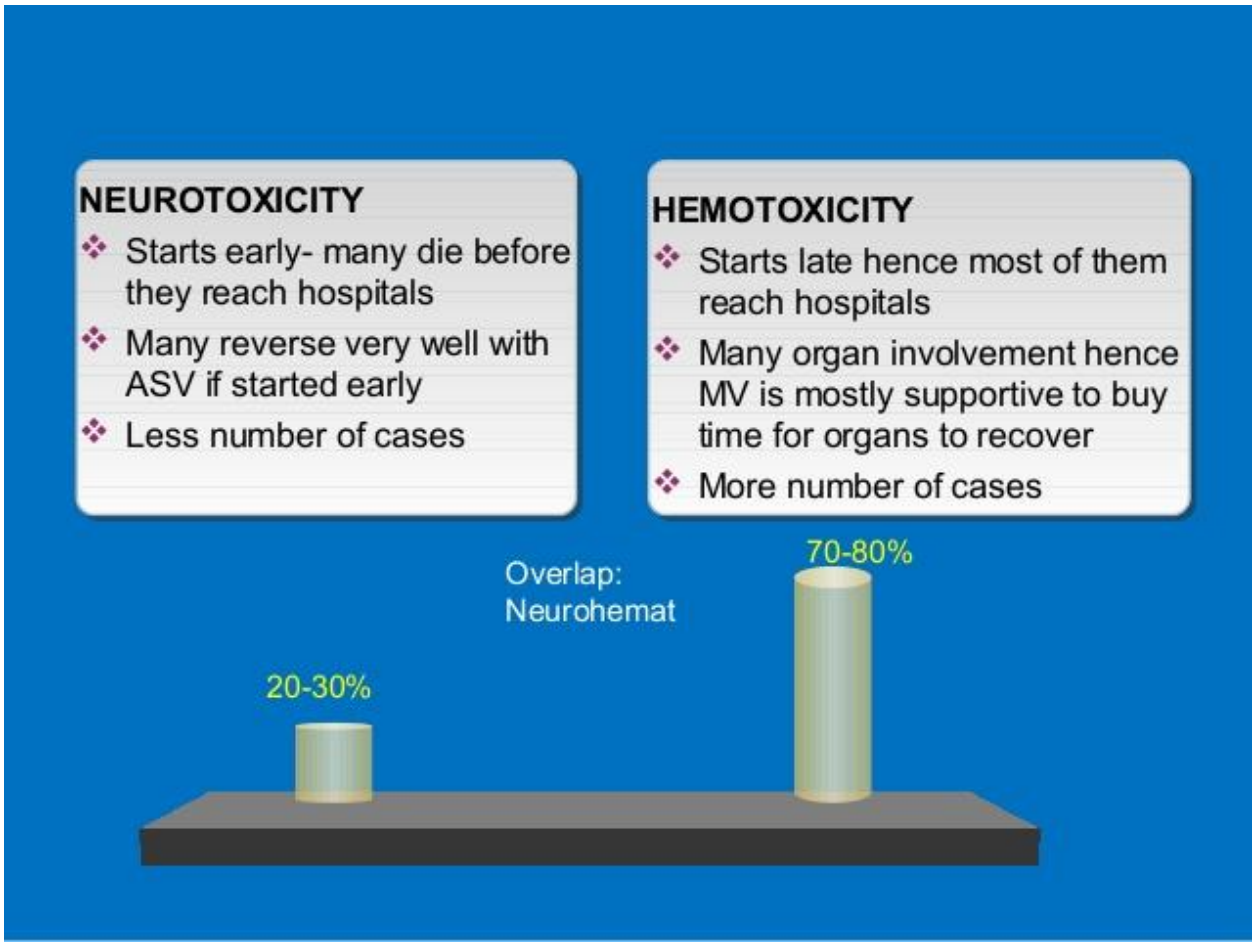
Syndrome 5

Paralysis with dark brown urine and acute kidney injury:

Bitten on land (with bleeding/clotting disturbance) **= Russell's viper, Sri Lanka or South India**

Bitten on land while sleeping indoors **= krait *(B. niger, B. candidus, B. multicinctus)*, Bangladesh, Thailand**

Bitten in sea, estuary and some freshwater lakes (no bleeding/clotting disturbances) **= sea snake**



" Anti venom, only effective antidote for venom. The essential part of treating systemic envenoming, but may be insufficient on own to save patient.

The given recommendation is that anti venom should be used only if patient has some benefit of anti venom are be considered to exceed the risk of reaction".

EPIDEMEOLOGY

"Mostly the incidence of snake-bites depends critically on the frequency of contact between snakes and humans. Except during rains, snakes are elusive and reclusive and so contact with humans is likely only when people move into the snakes' favoured environment".

"Example :

Rice fields in the case of Russell's vipers and cobras;

rubber and coffee plantations in the case of Malayan pit vipers)"

"Nocturnally active snakes are trodden upon by people walking along dark paths. Seasonal peaks of snake-bite incidence are usually associated with increases in agricultural activity or monsoon rains".

"Different species of snakes vary in their willingness to strike when disturbed. Typically7 "irritable" species include Russell's vipers (*Daboia russelii* and *D. siamensis*) and saw-scaled vipers (*Echis*)".

"Attacks may be inflicted in the home by peri-domestic species such as"

“cobras (*Naja*) which may live in roof spaces or under the floor and by kraits (*Bungarus*) which enter human dwellings at night in search of their prey like chicken but may bite people who move in their sleep”.

“The risk of envenoming after bites by venomous snakes varies with the species but is on an average it is about 50%. Bites in which the fangs pierce the skin but no envenoming results in a condition known as “dry bite”

“Epidemics of snake-bite may result from heavy flooding, as has been reported from India and Myanmar, and when the snakes’ habitat is invaded by a large workforce involved in road building or logging and as a result of irrigation plans that alter the climate making it attractive both for snakes and farmers”.

“There was no immediate increase in snake-bites in Myanmar after Cyclone Nargis but an increase was recorded in the aftermath 9-12 months later”.

“Males are more often bitten than females, but where the work force predominantly is females (e.g. tea and coffee picking). The peak age for bites is children and young adults”.

“There is some evidence that peak case fatality is in young children and the elderly. In pregnancy, snake-bite carries definite risks to mother and fetus,in the form of bleeding and abortion”.

“ Most snake-bites are inflicted on the feet and ankles of agricultural workers”.

CIRCUMSTANCES :

“Mostly snake-bites happen when the snake is pulled along, either in the dark or in undergrowth, by someone who is bare-footed or wearing sandals.”

“The snake may be picked up either unintentionally in a handful of foliage or intentionally by someone who is trying to show off.”

“Some bites occurs when the snake (usually a krait) comes in to the home at night in search of its prey (other snakes, lizards, frogs, mice) and someone sleeping on the floor rolls over onto the snake in their sleep. Not all the snake-bites happen in rural areas”.

“For example, in some large cities, such as Jammu in India, people”

“who sleep in small huts (*jhuggies*) are frequently bitten by kraits during sleep and wake with paralysis.”

“The risk of snake-bite is very strongly associated with Occupations like farming (rice), plantation work (rubber, coffee), herding, hunting, fishing and fish farming, catching and handling snakes for food (in snake restaurants), displaying and performing with snakes (snake charmers), manufacturing leather (especially sea snakes)”

“OCCUPATION AFFECTED

Farmers (rice)

Plantation workers (rubber, coffee)

Herdsmen

Hunters

Snake-handlers

Fishermen and fish farmers

Sea-snake catchers (for sea snake skins, leather)

IN INDIA”

“The numbers of snake-bite fatalities in India has long been controversial”.

“Estimates as low as 61 507 bites and 1,124 deaths in 2006 and 76,948 bites and 1,359 deaths in 2007 and as high as 50 000 deaths each year have been published”.

“The Registrar-General of India’s “Million Death Study” 2001-2003, is expected to provide reliable evidence of substantial mortality (exceeding 50 000 per year) because it is based on **R**epresentative, **R**e-sampled, **R**outine **H**ousehold **I**nterview of **M**ortality with **M**edical **E**valuation (“RHIME”)”

“ It covers all age groups across the entire country with geographical, seasonal and also occupational data”.

“Previous studies included a field survey in randomly selected villages in Barddhaman (Burdwan) district, West Bengal that suggested that among the total population of nearly five million people, around 8 000 with bites and 800 killed by snakes each year, an average incidence of 16.4 deaths/100 000/year . In Maharashtra State, between 1974-78, there were an average of 1 224 deaths/year (2.4 deaths/100 000/year)”

“Category 1:

CATEGORY 1	**Elapidae:** *Bungarus caeruleus; Naja kaouthia* (northeast), *Naja naja* (throughout)”
	“Viperidae: *Daboia russelii*, *Echis carinatus; Hypnale hypnale* (south-west)”

Category 2:

CATEGORY 2	**“Elapidae:** *Bungarus fasciatus, Bungarus niger, Bungarus sindanus, Bungarus walli; Naja oxiana”*
	“Viperidae: *Cryptelytrops albolabris*, *Cryptelytrops purpureomaculatus* (east), *Trimeresurus* (south-west), *Trimeresurus gramineus* (south India)”

“Death from snake-bite

Contributing factors”

“Factors identified as contributing to a fatal outcome included problems with antivenom use (inadequate dose or use of a monospecific antivenom of inappropriate specificity), delayed hospital treatment resulting from prolonged visits to traditional healers and problems with transportation, death on the way to hospital, inadequate artificial ventilation or failure to attempt such treatment, failure to treat hypovolaemia in shocked patients, airway obstruction, “

“complicating infections, and failure to observe patients closely after they were admitted to hospital”.

“Time between snake-bite and death

Although very rapid death after snake-bite has rarely been reported and it is clear that large series of snake-bite deaths that many hours usually elapse between bite and death in the case of elapid envenoming, and several days in the case of viper envenoming”

“SIGNS AND SYMPTOMS

Bites in which the fangs pierce the skin but no envenoming results are known as “*dry bites”.*

“The explanation for dry bites is either mechanical inefficiency of the venom apparatus striking at an unnatural angle (or through clothing) or perhaps voluntary retention of venom by the snake”

“Victims of snake-bite may suffer any or all of the following:

(1) Local envenoming”

"(2) Systemic envenoming

(3) Effects of anxiety prompted by the frightening experience of being bitten.

(4) Effects of first-aid and other pre-hospital treatments that may cause misleading results".

"Local symptoms and signs in the bitten part:

fang marks

local pain

local bleeding

bruising

lymphangitis (raised red lines tracking up the bitten limb)

lymph node enlargement

inflammation (swelling, redness, heat)

blistering

local infection, abscess formation

necrosis"

"Generalized (systemic) symptoms and signs

General"

“Nausea, vomiting, malaise, abdominal pain, weakness, drowsiness, Prostration”.

“Cardiovascular (Viperidae)

Visual disturbances, dizziness, faintness, collapse, shock, hypotension, cardiac arrhythmias, pulmonary oedema, conjunctival oedema (chemosis)”

“Bleeding and clotting disorders (Viperidae)

- Traumatic bleeding from recent wounds (including prolonged bleeding from the fang marks (venipunctures) and from old partly-healed wounds”

- “Spontaneous systemic bleeding - from gums, epistaxis, bleeding into the tears, intracranial haemorrhage (meningism from subarachnoid haemorrhage, lateralizing signs and/or coma from cerebral haemorrhage, haemoptysis, haematemesis), rectal bleeding or melaena, haematuria, vaginal bleeding, ante-partum haemorrhage in pregnant women, bleeding into the mucosae (e.g. conjunctivae), skin (petechiae, purpura, discoid haemorrhages – and ecchymoses) and retina”.

“Neurological features

“Cerebral arterial thrombosis (western Russell’s vi*per Daboia russelii)”*

“Thrombotic strokes, confirmed by neuro imaging, angiography, are reported rarely after envenoming”.

***“Neurotoxic* (Elapidae, Russell’s viper)**

Drowsiness, paraesthesiae, abnormalities of taste and smell, “heavy” eyelids, ptosis , external ophthalmoplegia(manifested as double vision), paralysis of facial muscles and other muscles innervated by lower cranial nerves, nasal voice or aphonia, regurgitation of feeds, difficulty in swallowing secretions, respiratory weakness and generalised flaccid quardriparesis”.

Skeletal muscle breakdown (sea snakes, some krait species – *Bungarus niger* and *B. candidus*, western Russell’s viper *Daboia russelii*)

Generalized pain, stiffness and tenderness of muscles, trismus, myoglobinuria, hyperkalaemia, cardiac arrest, acute renal failure.

Renal (Viperidae, sea snakes)”

“Loin (lower back) pain, haematuria, haemoglobinuria, myoglobinuria, oliguria/anuria, symptoms and signs of uraemia like acidotic breathing, hiccups, nausea, pleuritic chest pain etc”.,

“Endocrine features

Acute pituitary/adrenal insufficiency from infarction of the anterior pituitary (Russell’s viper in Myanmar and South India) due to pituitary apoplexy.”

“Acute phase: Shock, hypoglycaemia, seizures, altered sensorium
Chronic phase (months to years after the bite): Weakness, loss of secondary sexual hair, loss of libido, amenorrhoea, testicular atrophy, hypothyroidism, generalized lethargy, depressed mood etc”.

“Long-term complications (sequelae) of snake-bite

At the bite site, loss of tissue may result from sloughing or surgical débridement of necrotic areas. Amputation can occur. Chronic ulceration, infection, osteomyelitis, contractures, arthrodesis or arthritis may persist and causes severe physical disability”.

“Malignant transformation may occur in skin ulcers called marjolin’s ulcer (SCC)”

“Symptoms and signs of sea snake bites

Envenoming by sea snakes (Hydrophiinae) and sea kraits (Laticaudinae): unprovoked and bite is usually not painful and may not be noticed by the swimmer. Fangs and teeth may be left in the wound. There is minimal or no local swelling and there is no localized lymphadenopathy like in hemotoxic bites. Generalized rhabdomyolysis is the dominant effect of envenoming by these snakes although patients without this feature have been described”.

“ Earliest symptoms include headache and thirst.

Generalized aching, stiffness and tenderness of the muscles becomes noticeable between 30 minutes and 3½ hours after the bite.”

“Trismus can also occur. Even Passive stretching of the muscles is painful . Later, there is progressive flaccid paralysis starting with ptosis, as in other neurotoxic bites**.** The patient remains conscious until the respiratory muscles are sufficiently affected to cause respiratory failure”.

“Myoglobinaemia and myoglobinuria develops 3–8 hours after the bite**.** These are suspected when the serum appears brownish and the urine dark reddish brown (Coca-Cola-coloured). Bedside tests will appear positive for haemoglobinuria and myoglobinuria”.

“Myoglobin and potassium released from damaged skeletal muscles may cause” “renal failure, while hyperkalaemia developing within 6–12 hours of the bite may precipitate cardiac arrest”

“Venom composition

Around 90% of snake venom (dry weight) are proteins. Each venom contains a little more than a hundred different proteins: enzymes (constituting 80-90% of viperid and 25-60% of elapid venoms), non-enzymatic polypeptide toxins, non-toxic proteins such as nerve growth factor.”

Venom enzymes

These include hydrolases, hyaluronidase, and activators or inactivators of physiological processes, such as kininogenase. Most venoms contain l-amino acid oxidase, phosphor diesterases, 5’-nucleotidase, DNAase, NAD-nucleosidase, phospholipase A2 and peptidases.

Zinc metalloproteinase haemorrhagins: Damage vascular endothelium, causes bleeding.

Procoagulant enzymes:

- Venoms of Viperidae and some Elapidae contains serine proteases and procoagulant enzymes that are thrombin-like or activate factor X, prothrombin and other factors.
- The enzymes stimulate blood clotting with formation of fibrin in the blood”

- “This process results in incoagulable blood since most of the fibrin clot is broken down by the body’s own plasmin fibrinolytic system.
- Within 30 minutes of the bite, the levels of clotting factors are so depleted resulting in consumption coagulopathy.
- Some venoms contain multiple anti-haemostatic factors.

  For example, Russell’s viper venom contains toxins that activate factors V, X, IX and XIII, protein C, affects platelet aggregation and haemorrhage”.

“Phospholipase A2 (lecithinase): The most extensively studied of all venom enzymes. It damages mitochondria, erythrocytes, leucocytes, platelets, peripheral nerve endings, skeletal muscle,endothelium, and other membranes, produces presynaptic neurotoxic activity, opioid like sedative effects, leads to the autopharmacological release of histamine and anti-coagulants.

Acetylcholinesterase: Although found in most elapid venoms, it doesn’t contribute to the neurotoxicity”.

“Hyaluronidase: Promotes the spread of venom through tissues.Proteolytic enzymes like metalloproteinases, endopeptidases or hydrolases and polypetide cytotoxins”

“Increases vascular permeability causing oedema, blistering, bruising and necrosis at the bite site.”

“Venom polypeptide toxins (“neurotoxins”)

Postsynaptic (α) neurotoxins such as α-bungarotoxin and cobrotoxin, consists of 66-74 amino acids.

They bind to acetylcholine receptors at the motor endplate.

Presynaptic (β) neurotoxins such as β-bungarotoxin, crotoxin, and taipoxin, contain 120 amino acids and a phospholipase A subunit.

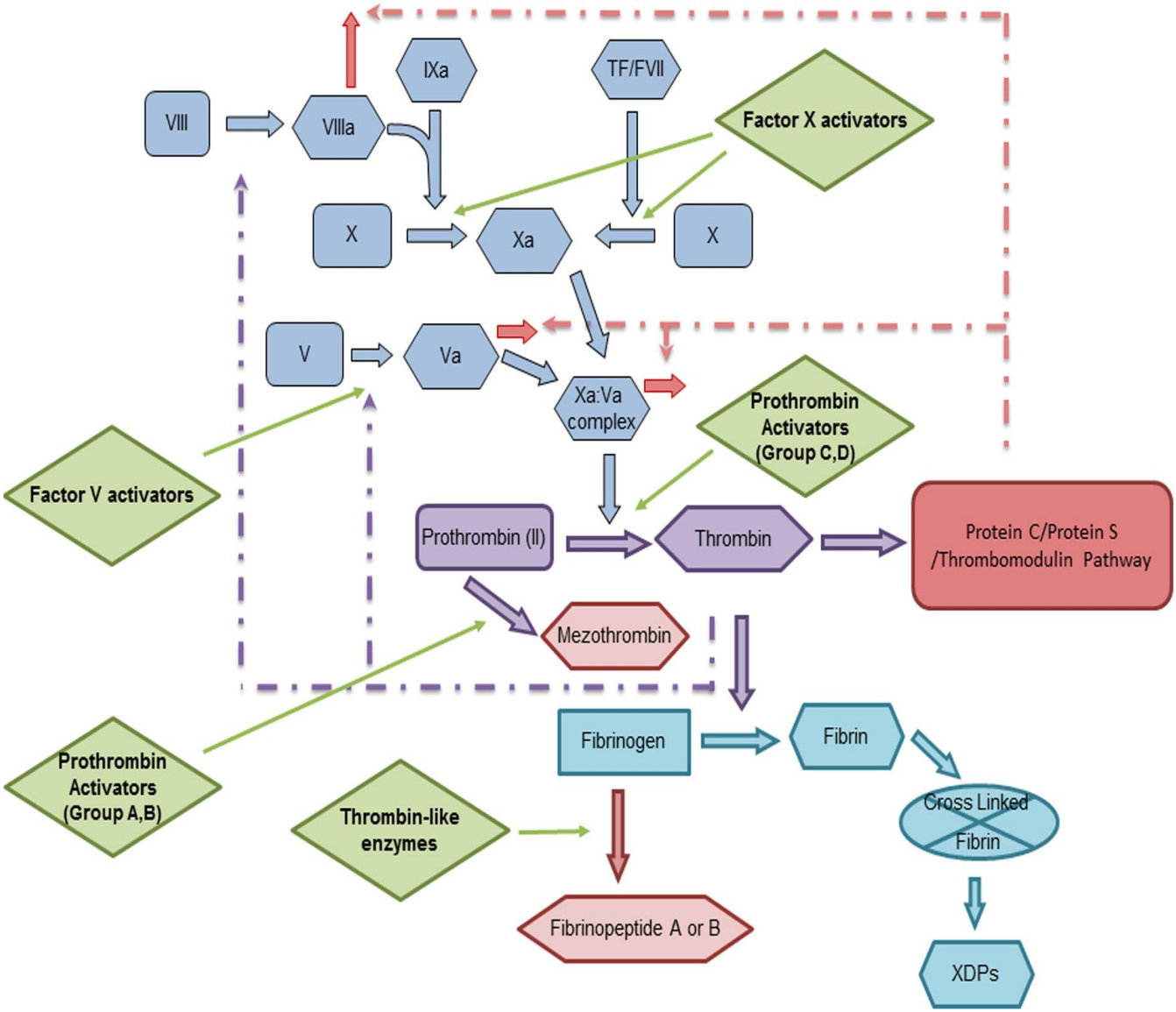
They release acetylcholine at neuromuscular junctions and then damage the endings, preventing further release of transmitter.”

“Quantity of venom injected at a bite, “dry bites”

- “Depends on the species and size of the snake, the mechanical efficiency of the bite, whether one or two fangs penetrated the skin and if there were repeated strikes. Either due to mechanical inefficiency or the snake’s control of venom discharge, a proportion of bites by venomous snakes does not result in the injection of sufficient amount to cause clinical effects”.

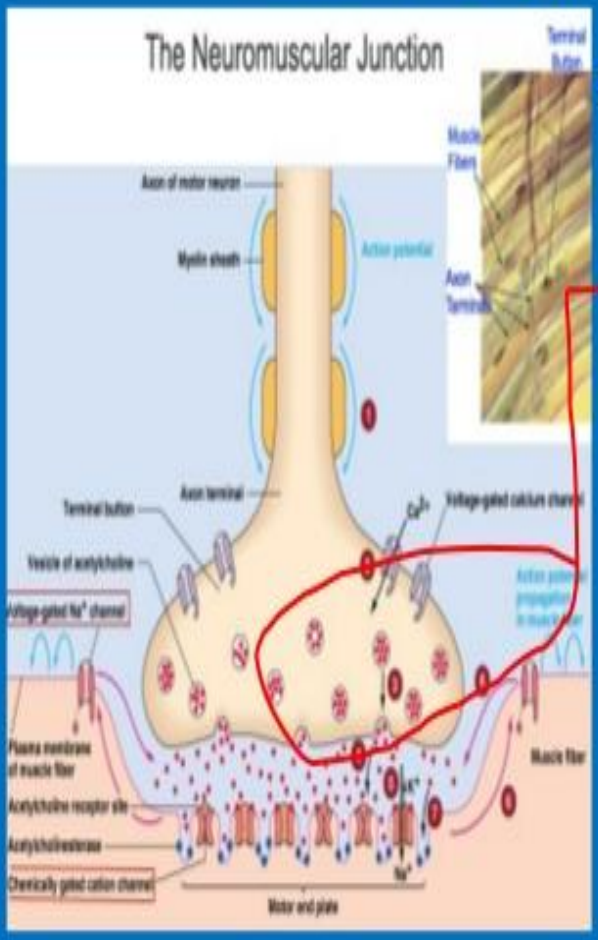
- “About 50% of bites by Malayan pit vipers and Russell’s vipers, 30% of bites by cobras and 5%-10% of bites by saw-scaled vipers does not result in any symptoms or signs of envenoming”.
- “Snake doesn’t exhaust the store of venom, even after several strikes, and they are still venomous after eating their prey”.
- Although large snakes tend to inject more venom than smaller specimens of the same species, the venom of young vipers may be richer in some dangerous components, causing more hemotoxicity.

Bites by small snakes should not be ignored or dismissed. They should be taken just as seriously as bites by large snakes of the same species.



"A schematic representation where each type of procoagulant toxin acts on the clotting pathway. Square shapes are inactivate factors, and hexagonal shapes are activated clotting factors. The blue arrows indicate conversion of inactive to active factors, and the red arrows indicate inactivation of the activated clotting factor".

Krait- Pre-synaptic action



Beta-bungarotoxin- Phospholipases A2

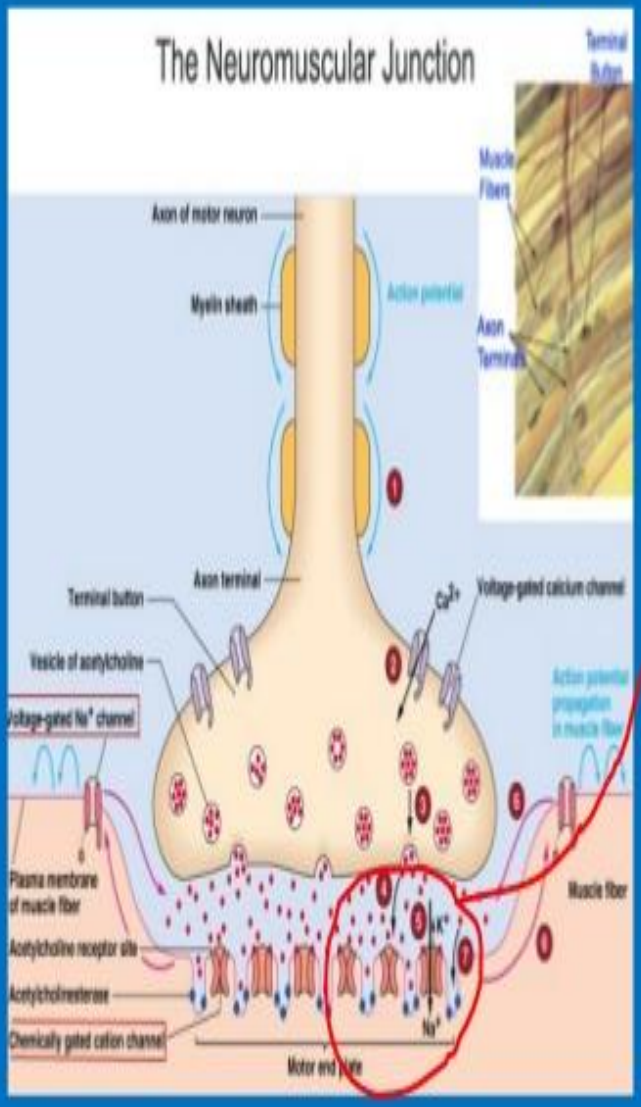
1) Inhibiting the release of Ach from the presynaptic membrane

2) Presynaptic nerve terminals exhibited signs of irreversible physical damage and are devoid of synaptic vesicles

3) ASV & anticholinesterases have no effect

Paralysis lasts several weeks and frequently requires prolonged MV. Recovery is dependent upon regeneration of the terminal axon.

Cobra – post-synaptic



- alpha-neurotoxins "Curare -mimetic toxins"
- Bind specifically to Ach receptors, preventing the interaction between Ach and receptors on postsynaptic membrane.
- Prevents the opening of the sodium channel associated with the Ach receptor and results in neuromuscular blockade.
- ASV -rapid reversal of paralysis.
- Dissociation of the toxin-receptor complex, which leads to a reversal of Paralysis

Anticholinesterases reverse the neuromuscular blockade

“Venom-Induced Consumption Coagulopathy

VICC is a simple term used to describe any coagulopathy resulting in the consumption of clotting factors due to a procoagulant toxin in venom. It can be caused by the bite of range of snakes including Viperid snakes, Elapidae snakes, and some”

“Colubrid snakes.

Before, the coagulopathy associated with snake envenoming was often referred to as a disseminated intravascular coagulation. However, the word disseminated intravascular coagulation is not appropriate for coagulopathy due to snakebite.

DIC results from widespread immune, endothelial, cellular, and clotting cascade activation and has a very high mortality, whereas VICC has a completely different pathogenesis (specific enzyme activation),and is also treated differently, with a much lower mortality.”

“Venom-induced consumption coagulopathy is characterized by the activation of the clotting pathway due to procoagulant toxins in the snake venom. They are referred to as procoagulant toxins because in vitro, they result in rapid clot formation, but in vivo, they lead to severe factor consumption and lead to bleeding risk.”

“The toxins differ between snake species and activate both extrinsic and intrinsic”

“pathway by targeting different clotting factors. Despite the differences, all procoagulant toxins cause a similar clinical picture of both clotting factor consumption and coagulopathy.”

“The clinical severity of VLCC dependent on which clotting factors are consumed. For example, a milder form appears to occur when there is only fibrinogen consumption,”

“whereas a more severe form is usually associated with multiple factor consumption, such as is seen with Australian elapid envenoming which results in fibrinogen, FV, FVIII consumption

But in Russell's viper envenoming with FV, FVIII, FX, and fibrinogen consumption”.

“The toxins in snake venom that produce VICC are classically categorized by where they act on the clotting pathway, with the most important ones being prothrombin activators, factor V and X activators, and thrombin-like enzymes (TLEs), the latter referred to as fibrinogenases”.

Prothrombin Activators

“Two large groups of snakes contain prothrombin activators:

Most of the Australasian elapids (brown snake [Pseudechis spp], tiger snakes [Notechis spp], rough-scaled snake [Tropidechis carinatus], broad-headed snakes”

“[Hoplocephalus spp], and taipans [Oxyuranus spp]) and the Echis genus, which includes carpet vipers and the sawscaled viper.

Prothrombin activators is classified into 4 groups (A-D) depending on their structure, function, and cofactor requirements.”

“Australian snakes contains the group C and D prothrombin activators which are serine proteases. Group C prothrombin activators are found in the brown snake and taipan and resemble the human prothrombinase complex or factor Xa Va complex which converts prothrombin to thrombin as in extrinsic pathway”.

“Group D toxins are found in tiger snake, rough-scale snake, and broadheaded snakes and contain a toxin similar to human factor FXa,without the FVa cofactor.”

“Group A and B toxins are found in the Echis species of snakes and directly activated prothrombin but convert it to meizothrombin rather than the fully active thrombin.”

“Activation of the clotting cascade by prothrombin activators results in multiple factor deficiencies due to the positive and negative feedback loops activated when prothrombin (II) is converted to thrombin (IIa)”

“This leads to activation of FV to FVa and FVIII to FVIIIa regardless of whether the initial toxin contained an FVa-like complex or not.”

“Thrombin also activates fibrinogen to fibrin consuming all of the fibrinogen complex.

Measurements of factor levels after envenoming have shown severe deficiencies of factor V and factor VIII, with an associated not recordable prothrombin time (PT)/international normalized ratio (INR) with an undetectable fibrinogen levels, consistent with fullb lown”

VICC.

“A partial VICC has been recognized in patients with low, but recordable fibrinogen levels where the pathway has not been activated completely and not all of the fibrinogen has been converted to fibrin”.

“Factor X and V Activators Russell's viper (Daboia genus) venom contains factor V and X activators. Most important toxin is the factor X activator, which converts factor X to Xa resulting in the formation of the prothrombinase complex and subsequent conversion of fibrinogen to fibrin”.

“Because the factor X activation acts earlier in the coagulation pathway (before common pathway), it results in positive and negative feedback loops leading to indirect consumption of factors V and VIII.”

“There is also direct activation and consumption of factor V. This again results in not recordable PT/INR and undetectable fibrinogen.”

Thrombin-Like Enzymes

"Thrombin-like enzymes are different to the prothrombin activators and factor Xa/Va activator toxins because they simply consume fibrinogen rather than activating the clotting pathway. For this reason,

TLEs only produce an isolated deficiency of fibrinogen and uncommonly affects other clotting factors.

They usually cause a milder form of VICC, but they will result in non recordable PT/INR and bleeding complications if there is undetectable fibrinogen.

There are more than 67 different TLE toxins that have been identified, mostly being zinc

metalloproteinase that cleaves the α chain of fibrinogen resulting in consumption of fibrinogen without the production of (or conversion to) fibrin.

Other TLEs cleave the β chain and a few cleave both chains, but they do not result in intact fibrin."

" Ancrod is the best known of the TLEs and was for a while tested for use in cerebrovascular disease, until it was shown that there were many bleeding complications".

Clinical Manifestations of VICC

"The clinical outcome for patients who develops VICC is not only dependent on the severity of the coagulopathy, but other factors such as trauma, platelet count and function, and vascular injury are important.

Arguably the most important issues in patients with VICC is whether physical trauma occurs and anything that potentially causes vessel damage and the release of tissue factor may result in hemorrhage.

This may result in significant morbidity or death in case of intracranial or major organ hemorrhage. Bleeding can range from minor, such as oozing at the bite site or cannula insertion site, to major life-threatening hemorrhage requiring blood transfusion."

"Intracranial hemorrhage can be seen after an associated head injury, but spontaneous bleeds also occur, often in the setting of hypertension.

Thoracic cavity bleeding or bleeding into other body compartments can occur after trauma".

"The metalloproteinase prothrombin activator toxin ecarin found in Echis species not only activates the clotting pathway but also acts as a hemorrhagin. These hemorrhagins are proteolytic enzymes that causes damage to the blood vessel wall, affecting the basement membrane and creating a "shear-stress"–like injury which, in turn, increases"

“the risk of bleeding associated with VICC.

This explains why spontaneous and more severe bleeding is reported with Echis envenoming compared with Australian elapid envenoming, despite the prothrombin”

activators being more potent in the latter.

“The duration of VICC depends on the type of toxin and the administration of antivenom.”

“Venom-induced consumption coagulopathy resulting from Australian elapid envenoming appears to resolve after 24 to 48 hours independent of antivenom treatment, and the time to recovery appears to depend only on the production of new clotting factors”.

“ On the other hand, Echis-induced VICC has been shown to continue for days if not treated with antivenom. However, after Echis envenoming is treated with antivenom, the time of recovery is also 24 to 48 hours demonstrating that once the toxin is neutralized, there is normal recovery of clotting factors.”

An understanding of expected natural course of VICC is determined by the type of snake and procoagulant toxins which may influence the need for antivenom, duration of

Hazard, reduction for trauma, and decision to use factor replacement.

Other Hematologic Consequences of Snakebite

Anticoagulant Coagulopathy

A less common condition related to snake envenoming is an anticoagulant-type coagulopathy. The Australian black snake (Pseudechis) genus venom has been shown to inhibit clotting in vitro and cause a mild to moderate elevation of the aPTT. In a series of

17 mulga snake envenomings in Australia, 10 patients developed an anticoagulant coagulopathy evidenced by an aPTT median rise of 82 seconds (interquartile range, 55-91 seconds). Four of these patients had a small INR rise (b3.0), with the rest having an INR within the normal limits. Fibrinogen and D-dimer levels were normal.

No patients developed any significant clinical bleeding, supporting the idea that this is

not a significant coagulopathy. A similar anticoagulant coagulopathy was also found in red-bellied black snake (Pseudechis porphyriacus) bites.

Although this anticoagulant coagulopathy is unlikely to be clinically important, any subtle elevation in aPTT is an early indicator of envenoming and hence a useful marker in identifying envenoming early. This means that antivenom can be given early based on this. In the case of black snake envenoming, which can cause myotoxicity,

The early administration of antivenom has been shown to prevent myotoxicity. The occurrence of anticoagulant coagulopathies in other snakes remains unclear, mainly because the 20-minute WBCT is unlikely to be abnormal, except in the most severe cases. Anticoagulant toxins have been identified in a number of snakes, including cobras (Naja spp) and the southern copperhead (Agkistrodon genus). The venom of the southern copperhead contains a protein C activator, but does not appear to have any clinical effects in humans.

Thrombotic Microangiopathy

A proportion of patients who develop VICC can also go on to develop an envenoming-related thrombotic microangiopathy, of which the pathogenesis is not completely understood. This is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and an acute kidney injury which continues beyond the resolution of VICC

and has been noted in a number of different snake species, including Australasian elapids and many viper species. From the information available in cases, it is difficult to define where snakebite-induced thrombotic microangiopathy fits on the spectrum

of microangiopathy—thrombotic thrombocytopenic purpura or hemolytic

uremic syndrome—and it is likely to be a distinct syndrome. The combination of thrombocytopenia with mainly renal involvement is unusual.

In the full blown syndrome which occurs in less than 5% of cases, patients develop severe thrombocytopenia and acute anuric renal failure requiring renal replacement therapy for 2 to 6 weeks. However, most cases are less severe and snakebite-induced thrombotic microangiopathy appears to be a spectrum of disorders, with some patients only having a brief period of thrombocytopenia and a moderate rise in creatinine

without oliguria.

Treatment is supportive in all cases, with renal replacement therapy being the most important intervention in severe cases. Plasmapheresis has been used in a number of more severe cases but does not appear to change the natural course of the thrombocytopenia, anemia, or renal injury. The lack of benefit of plasmapheresis is probably due to the underlying cause being different and not related to ADAMTS-13

function or antibodies like in thrombotic thrombocytopenic purpura.

An important consideration is that plasmapheresis will remove the antivenom. It is unclear whether antivenom alters the course of thrombotic microangiopathy, but is potentially beneficial for any toxin-related injury resulting in the neutralization and removal of the toxin to prevent or improve the syndrome.

ACUTE KIDNEY INJURY PATHOGENESIS :

It is mainly observed in snakes which belong to the viperidae group and it is seen less with sea snake bites and bites of colubridae group. Most of the Indians are victims of Russell's viper or echiscarinatus bites, which causes AKI.

It is an important complication of snake bite and a proper supportive management after the antivenom administration is of utmost importance for a good patient outcome.

Tubular necrosis and cortical necrosis are the important causes of renal failure. The renal failure after bite is usually reversible, but if acute cortical necrosis occurs, it may lead to an incomplete recovery.

The main cause of this "unacceptable incidence" of snake bite fatalities is becausepeople try out bizarre remedies initially instead of going to a primary health care.

There are very less number of studies on the development and outcome of AKI following snake bite in India.

The exact pathogenesis for ARF is not well established. However a number of factors contribute like

- Bleeding causing hypotension
- Circulatory collapse

- Disseminated intravascular coagulation
- Intravascular hemolysis
- Nephrotoxicity of the venom
- Nephrotoxic drugs in treatment
- Cellulitis causing myoglobinuria and tubular necrosis
- Acute interstitial nephritis is also described

Albuminuria can be present in most of the cases. This shows that the toxin induced breakdown of the renal filtration barrier. However, this finding is more useful in followup of these patients as a persistent albuminuria can serve as a marker of residual renal dysfunction after recovery from acute kidney injury. Other common findings would be thrombocytopenia, metabolic acidosis and coagulopathy is itself an independent marker since it is an indirect marker for damaged renal vasculature.

RHABDOMYOLYSIS

The entity rhabdomyolysis associated with acute renal failure is to underlie three basic mechanisms.

- Renal vasoconstriction
- Direct heme protein induced cytotoxicity
- Intraluminal cast formation and tubular obstruction

Renal vasoconstriction : it is a characterstic feature of myoglobinuric AKI and it can be explained by several mechanisms. First, when there is extensive myonecrosis there is fluid accumulation in third space and resultant intravascular volume depletion (IVF)

and aggressive vasoconstriction. Secondly, there is generation of endotoxins like endothelin-1, thromboxane A2, TNF-alfa and they activate endotoxin cytotoxin cascade resulting in vasoconstriction. Thirdly, nitric oxide, a potent endogenous vasodilator is scavenged by the heme protein myoglobin. In the setting of myoglobinuria, renal hypoperfusion is exacerbated because myoglobin in the setting of myoglobinemia, can cause increase in peripheral vascular resistance. Thus hypovolemia cold not be detected clinically and ischemic tissue injury is aggravated.

Moreover, renal vasoconstriction can facilitate heme toxicity by decreasing GFR and prolonging their half life, promoting proximal tubular uptake and increasing the propensity for cast formation. IV volume depletion stimulates fluid reabsorption in tubules and increases intraluminal myoglobin concentration, favors cast deposition, tubular obstructuion.

Myoglobin mediated proximal tubular cytotoxicity : heme proteins and myoglobin have a direct cytotoxic effect on proximal tubules. Heme proteins can exacerbate ischemic renal injury by intesyfying renal vasoconstricton in the setting of volume depletion.

They decrease ATP availability via non hemodynamic iron mediated mechanism. Heme protein endocytosis by the proximal tubular cells directly sensitizes the plasma membrane to phospholipase A2 mediated injury in ischemia-reperfusion. Myoglobin contains iron as a ferrous oxide (Fe2+) necessary for blinding with oxygen.However oxidation of ferrous to ferric oxide generates hydroxyl radical that can injure tubular epithelium.

This is further strengthened by the experiments where iron chelators (desferoxamine) and antioxidants like glutathione have shown protective effect in myoglobinuria induced tubular damage.

Myoglobin itself exhibit peroxidase like enzyme activity and leads to uncontrolled oxidation of biomolecules, lipid peroxidation and generation of isoprostanes.

Intraluminal cast formation and tubular obstruction : Heme protein cast formation and tubular obstruction primarily occurs in distal tubules. Acidic urine, high concentration of myoglobin and the presence of tamm-horsfall protein largely

determine formation of tubular casts. Second most important factor is acidic urine. In acidic pH solubility of myoglobin is decreased and it forms aggregates.
Since, tamm horsfall proteins are primarily synthesized in distal tubules and stasis of myoglobin occurs more in distal tubules, they become primary location for cast formation and resultant and tubular obstruction.

Additional mechanisms of myoglobinuric acute renal injury are :

1. Hyperphosphatemia potentiating ischemic and nephrotoxic damage
2. Hyperuricemia contributes to cast formation and distal tubule obstruction
3. Severe crush injury and rhabdomyolysis triggers disseminated IV coagulation and results in intrarenal micro thrombus formation and aggravation of ischemic damage

Rhabdomyslysis and its link with elevated CPK :

- ✓ The sarcolemma contains numerous pumps that regulate cellular electrochemical gradient.
- ✓ This gradient maintains electronegativity within cell, for which ATP is used as an energy source.
- ✓ Rhabdomyolysis causes ATP depletion distrupts cellular transport leads to elevated intracellular calcium level, activation of proteases and leakage of

- ✓ CREATININE KINASE, potassium, phosphate, and myoglobin
- ✓ Muscle damage is further amplified by infiltration of neutrophils
- ✓ Ferrihemate produced from myoglobin at acidic pH produces free radicals and direct nephrotoxicity.
- ✓ These proteins may enhance vasoconstriction through interactions with nitric oxide and endothelin.

Thereby causing **AKI**

Renal pathology

Tubulointerstitial lesions, predominantly acute tubular necrosis,are observed in 70% - 80% of patients with acute renal failure.

Biopsies performed during the first week after envenoming reveal dilated tubules lined by flattened epithelium and, in severe cases, tubulorrhexis with cell necrosis and desquamation of the necrotic cells from the basement membrane. The tubular lumina sometimes contain hyaline or hemoglobin pigment casts. Varying degrees of interstitial edema, inflammatory cell infiltration, and scattered areas of hemorrhage can be present. Biopsies done later reveal regenerating tubular epithelium and granular casts in the lumen.

Myoglobin casts are seen in patients bitten by the sea snake or the Australian small-eyed black snake Some studies been have carried out detailed ultrastructural analyses of renal tissue from patients with ARF from snake bites.

Electron microscopy reveals dense intracytoplasmic bodies representing degenerating organelles in the proximal tubules, with areas of denudation of the basement membrane.

Distal tubular cells show a dilated endoplasmic reticulum and many degenerating organelles. Some tubules are completely acellular, consisting of only a collapsed basement membrane.

The interstitium is infiltrated with eosinophils, mast cells, plasma cells, lymphocytes, and some hyperplastic fibroblasts. Mast cells and eosinophils show both granulated and partially degranulated forms. Thus the lesions arising from snakebite- induced ARF differ from those observed in acute tubular necrosis due to other causes. Features unique to snake-bite induced ARF are the severe tubular and vascular lesions,

increased apoptosis (defined as accelerated physiologic cell death) in the distal tubules, and in the presence in the interstitium of eosinophils, mast cells, and hyperplastic fibroblasts.

Acute interstitial nephritis alone has been observed by us in some patients following Echis carinatus bite and in some patients following Russell's viper bite. A recent report from India described renal papillary necrosis, but the species of snake causing the lesion was not identified.

Two instances of necrotizing arteritis of the interlobular arteries have occurred in association with acute tubular necrosis secondary to Russell's viper bite. Thrombophlebitis of the arcuate vein and its tributaries also was present in these patients.

Dense deposits of C3 were seen in the walls of afferent and efferent arterioles in these cases, but the significance of this 12% of all cases of cortical necrosis in some studies.

The renal lesion that carries the most sinister prognosis is documented in patients bitten by Russell's viper, Echis canacute cortical necrosis.

Snake bite the second most natus, Agkistrodon hypnale, and bothrops species common cause of acute cortical necrosis in India.

Cortical necrosis can be patchy or diffuse. Autopsy specimens showing diffuse cortical necrosis disclosed a narrow subcapsular zone containing a few tubules and and occasional glomerulus that appeared normal.

This zone overlay a broad ischemic area occupying most of the cortex. In this ischemic area, only the outline of the glomeruli and the tubules could be discerned.

Fibrinoid necrosis and occlusive thrombosis were seen in lobar and sublobar arteries in about 20% of cases.

Fibrin thrombi were observed in the glomerular capillaries in 10% to 25%. The ischemic zone was separated from the medulla by a zone of tissue that appeared hyperemic and contained a dense leukocytic infiltrate.

The deeper cortical and medullary regions showed changes of extensive tubular necrosis. The histologic changes varied with the duration of illness.

Evidence of healing was seen in the form of fibroblastic proliferation, organization of arterial and arteriolar thrombi, and fibrosis of the arterial wall.

Calcification on either side of the necrotic zone (subcapsular as well as corticomedullary) could be seen both in early and late stages of the infarct.

In biopsy specimens showing patchy cortical necrosis, varying numbers of glomeruli were found to be necrotic.

Renal ultrastructure in cortical necrosis following Russell's viper bite has been reported in few patients.

In one patient who was biopsied 10 days after envenomation, the glomeruli showed collapsed capillary basement membrane denuded of epithelial cells and foot processes. The urinary space was filled with erythrocytes, neutrophils, degenerating epithelial cell cytoplasm, and fibrin. No viable endothelial or mesangial cells were identifiable in the tuft, but swollen rounded cell.. Fibrinoid

necrosis of arterioles and fibrin thrombi are seen mostly of endothelial origin, were present in some capillary loops.

No platelets were visible.

Tubules showed an intact basement membrane surrounding degenerating epithelium, erythrocytes, and leukocytes.

Endothelial swelling of small arterioles and necrosis of peritubular capillaries also were

evident in this patient.

In the second patient, the biopsy was performed 31 days after the bite.

The urinary space contained unidentified cells with large cytoplasmic vacuoles but no erythrocytes.

The cortical tubules were lined by flattened epithelium with large nuclei and a dilated endoplasmic reticulum.

The tubular basement membrane was thickened, and fibroblastic proliferation was seen in the interstitium.

Sitprija and Boonpucknavig have found electron-dense mesangial deposits by electron microscopy even in the absence of renal failure in patients bitten by cobras and green pit vipers.

In green pit viper envenoming, fibrin thrombi and degenerating platelets have been observed in the glomerular capillaries.

Immunofluorescence data are scanty; Sitprija and colleagues demonstrated granular deposits of C3 without any immunoglobulins in the glomerular mesangium and arterial walls in 2 patients with acute renal failure following Russell's viper bite.

Investigations/laboratory tests

20-minute whole blood clotting test (20minCT)

This useful and informative bedside test requires very little skill and one piece of apparatus – clean, dry, glass vessel (tube or bottle).

Method

Place 2 ml of fresh sampled venous blood in a small, new or heat cleaned, dry, glass tube.

Leave undisturbed for 20 minutes at room temperature.

Tip the vessel once.

If the blood is still liquid (unclotted) and moves out, the patient has hypofibrinogenaemia ("not clotted blood") as a result of venom-induced consumption coagulopathy.

In the South-East Asia region, not clotted blood is diagnostic of a viper bite and rules out elapid bite.

If the vessel used is not made of an ordinary glass, or if it has been cleaned with a detergent, it may not stimulate clotting of the blood sample (surface activation of factor XI – Hageman factor) and test will not be valid

If there is any doubt, repeat the test again, including a "control" like blood from a healthy person such as a relative

Sometimes - in West Papua and the Maluku Islands, envenoming by elapids can cause not clotted blood sample.

Other tests

Haemoglobin concentration/haematocrit:

A transient increase in haemoconcentration resulting from a generalized increase in capillary permeability (e.g. in Russell's viper). Most commonly, there is a

decrease reflecting blood loss or, in the case of Indian, Thai or Sri Lankan Russell's viper bite, intravascular haemolysis.

Platelet count:

Counts may be decreased in victims of envenoming by vipers and Australasian elapids.

White blood cell count:

There is early neutrophil leucocytosis is evidence of systemic envenoming from any species.

Blood film:

Peripheral smear should be examined for fragmented red cells ("helmet cell", schistocytes) when there is microangiopathic haemolysis.

Plasma/serum:

It can be pinkish or brownish if there is massive haemoglobinaemia or myoglobinaemia.

Other Biochemical abnormalities:

Aminotransferases and muscle enzymes (creatine kinase, aldolase etc) will be elevated if there are severe local muscle damage or, specifically, if there is generalized muscle damage (sea snake, some krait, Australasian elapid and Sri Lankan and South Indian Russell's viper bites).

Mild hepatic dysfunction is reflected in slight increase in other serum enzymes. Bilirubin is increased following massive extravasation of blood.

Serum Potassium, creatinine, urea or blood urea nitrogen levels are raised in acute kidney injury of Russell's viper, hump-nosed viper bites and other sea snakebites.

Early potassium change may be seen following extensive rhabdomyolysis in sea snake-bites.

Bicarbonate will be low when there is metabolic acidosis (e.g. renal failure).

Hyponatraemia (transient) is reported in victims of krait bites in northern Vietnam (*Bungarus candidus and B. multicinctus*) due to SIADH or hypopituitarism

Arterial blood gases and pH

It may show evidence of respiratory failure (neurotoxic envenoming) and acidaemia (respiratory or metabolic acidosis).

Contra indication: Arterial puncture is contraindicated in patients with coagulation abnormalities (Viperidae and some Australasian Elapidae)

Saturation:

Oxygen saturation can be assessed non-invasively in patients with respiratory failure or shock using pulse oximeter.

Urine examination:

The colour of the urine (pink, red, brown, black) should be examined and it should be tested by dipsticks for blood or haemoglobin or myoglobin.

Standard dipsticks doesn't distinguish blood from haemoglobin and myoglobin. Haemoglobin and myoglobin can be separated by immunoassays but it is not a easy or reliable test.

Microscopic examinaation will confirm whether there are erythrocytes in the urine. Red cell casts indicate glomerular involvement.

Massive proteinuria is an early sign of the increase in capillary permeability in Russell's viper envenoming and an early sign of acute kidney injury.

Investigations for VICC

The diagnosis of VICC is made based on a history of and evidence of coagulopathy due to factor defeciency. This can be confirmed by an abnormal

(often not recordable) INR, or PT, lower undetectable fibrinogen and an elevated D-dimer (at least 10 times the upper
limit)

This definition captures all forms of VICC, from the milder TLE-induced fibrinogen consumption to the more severe factor consumption, seen with prothrombin activator venoms.

Fibrinogen is the most persistently consumed factor in all types of bites causing VICC because it is a common point of both the pathways.

The D-dimer is marker of fibrin degradation from formed cross-linked fibrin clot. Therefore, D-dimer levels are expected to be markedly increased in VICC resulting from procoagulant toxins that activate clotting pathway high up.

In this case, normal fibrin is formed from fibrinogen cross-linked by factor XIII and degraded by plasminogen. In the case of Australian elapids, the values are 100 to 1000 times the upper limit of normal.

For Russell's viper bite, the D-dimer is elevated by 10 to 100 times the upper limit of normal. For the Thrombin Like Enzymes which consume fibrinogen without the production of fibrin, and so there is no formation of cross-linked fibrin there is only a modest elevation of the D-dimer.

The reason for an abnormal D-dimer with this situation is unclear but may be due to the D-dimer assay being less specific, with large concentrations of non–cross-

linked fibrinogen degradation products (FDPs) or to some associated endogenous activation of the clotting pathway.

A less specific marker of fibrinogen degradation products, FnDP/FgD or FDP assay, will be 100 times normal in VICC due to TLEs. With only a modest increase in the D-dimer values.

However, these FDP assays are no longer available in diagnostic labs, which is unfortunate for regions where snakes with TLEs occur. The Serial measurement of fibrinogen levels has been used in many studies to demonstrate that the recovery of coagulopathy and is a useful endpoint for research into VICC. Clinically, the measurement of fibrinogen in VICC will confirm that there has been consumption but will not usually add much to the additional information to a PT/INR or D-dimer.

Fibrinogen is the slowest of all factors to recover, and effective clotting appears to occur with only minimal fibrinogen recovery to 0.5 to 1.0 g/L when the PT/INR values has almost been normalized. This means that it is not a good clinical marker of recovery. The PT/INR is a more useful marker of recovery of VICC because it measures the functional recovery of the clotting pathway and clinicians better understand the risk of bleeding associated with increased INRs.

Bedside assessment of clotting function in VICC is ultimately the best tool, but there continues to be no single reliable and accurate bedside test for the diagnosis

of VICC. The whole blood clotting test (WBCT) is the most commonly used bedside clotting test countrywide. This test works on the principle that blood taken from a patient with VICC is not clotted and so will not clot in a glass tube within a defined time frame, usually

20 minutes at ambient temperature.

Although widely used, there is no standardized procedure for the WBCT, and so, the test is a mislead with errors, misinterpretation, and high false-negativity rates in a busy clinical environment, which is prone to interruption and distraction.

Various studies have used end points of 10, 15, 20, and 30 minutes, and there is no universally agreed tube for collection or defined volume of blood to be collected.

A recent study of the 20-minuteWBCT in patients with Russell's viper bite showed a sensitivity of only 42%, which contributes to delays in antivenom administration. However, it has been suggested that when performed under strict guidelines, the WBCT may be more than accurate and further studies are required to confirm this findings.

Modern point-of-care (POC) INR testing devices have also been used in patients with VICC. Unfortunately, POC INR machines have also been not reliable and have also been shown to have a high false-negative rate in Australian snakebites and cannot be recommended for use.

In a small study of 15 patients, the POC INR was normal in 3 of 7 patients with VICC where a laboratory INR was not recordable.

The reason for this, lies in the difference between the assays from formal laboratories and POC machines.

A standard laboratory PT is measured by adding thromboplastin (tissue factor) to plasma and calculating the time to clot formation by usually identifying a clot by either spectrophotometry/fibrometery (mechanical).

In contrast, POC INR machines does not assesses or measure clot formation, but use thrombin cleavage as a marker of clotting function.

This is achieved by adding tissue factor to a blood sample (similar to laboratory method) to trigger clot formation and then adding an electrochemical substrate which is activated when it is cleaved by the thrombin.

In patients with VICC where factor deficiencies prevent clot formation, there still remains active thrombin, due to activation by the prothrombin activator. Therefore the substrate in POC machines is still able to be cleaved and activated, incorrectly detecting clot formation.

This means that in patients with VICC, a POC INR will often give a normal INR result when in fact the PT/INR is not recordable when repeated in the laboratory.

FIRST AID TREATMENT

Recommended Method for India

The first aid being currently recommended is based around the mnemonic:

"Do it R.I.G.H.T."

It consists of the following:

- ☑ **R. =** **Reassure the patient. 70% of all snakebites are from non-venomous species. Only 50% of bites by venomous species actually envenomate the patient**
- ☑ **I =** **Immobilise in the same way as a fractured limb. Use bandages or cloth to hold the splints, not to block the blood supply or apply pressure. Do not apply any compression in the form of tight ligatures, they don't work and can be dangerous!**
- ☑ **G. H. =** **Get to Hospital Immediately. Traditional remedies have NO PROVEN benefit in treating snakebite.**
- ☑ **T=** **Tell the doctor of any systemic symptoms such as ptosis that manifest on the way to hospital.**

ANTIVENOM

Antivenom treatment for snake-bite was first introduced by Albert Calmette

at the Institute.

Antivenom is immunoglobulin, usually pepsin-refined F(ab')2 fragment of whole IgG purified from the plasma of horse, mule or a donkey or sheep (ovine) that has been immunized with the venoms of more than one species of snake.

'Specific' antivenom, implies that it has been raised against the venom of the snake which has bitten the patient and that it can therefore be expected to contain specific antibodies that will neutralize that particular venom and also the venoms of closely related species (paraspecific effect).

Monovalent antivenom neutralizes the venom of one species of snake. Polyvalent (polyspecific) antivenom neutralizes the venom of different species of snakes, usually the important species, in a particular geographical area.

For example, the Indian manufacturers' 'polyvalent anti venom' is raised in horses using the venoms of the four important venomous snakes in India (Cobra, *Naja naja*; Indian krait, *Bungarus caeruleus*; Russell's viper, *Daboia russelii*; saw-scaled viper, *Echis carinatus*),

Although the validity of concept of "the big four" is increasingly challenged by discovery of other species that are also important in certain regions

Example. *H. hypnale* in South-West India *Trimeresurus malabaricus* in southern India; *Echis carinatus sochureki* in Rajasthan.

Antivenom reactions:

A proportion, usually more than 10%, develop a reaction either early (within a few hours) or late (five days or more) after being given antivenom.

The risk of reactions is dose-related, except in rare cases in which there has been sensitization (IgE Type I hypersensitivity) by previous exposure to serum, example, to equine or tetanus-immunoglobulin or rabies immunoglobulin.

(1) ***Early anaphylactic reactions***: Usually within 10 minutes to 3 hours of starting antivenom, the patient begins to itch (over the scalp) and develops urticaria, dry cough, fever, nausea, vomiting, abdominal colic, diarrhoea and tachycardia.

A minority of these patients can develop severe life-threatening reactions hypotension, bronchospasm and angio-oedema.

Fatal reactions are probably been under-reported as death after snake-bite is usually attributed to the venom and patients may not be monitored carefully after treatment.

Mostly, these reactions may not be truly "allergic", because, these are not IgE-mediated type I hypersensitivity reactions to horse proteins as there are no evidence of specific IgE, either by skin testing or radioallergosorbent test (RAST). Complement activation by IgG aggregates/ residual Fc fragments or by direct stimulation of mast cells and basophils by antivenom protein are more likely mechanisms for all these reactions.

(2) ***Pyrogenic (endotoxin) reactions:*** Usually these develop 1-2 hours after antivenom treatment. Symptoms include shaking chills (rigors), fever, and a fall in blood pressure(due to vasodilatation)

Febrile convulsions may be precipitated in children.

These reactions are caused by pyrogen contamination during the manufacturing process. They are commonly reported.

(3) ***Late (serum sickness type) reactions:*** Develop 1-12 (mean 7) days after treatment. Clinical features include low grade fever, nausea, vomiting, loose stools, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swelling, mononeuritis multiplex, proteinuria with immune complex nephritis.

Patients who suffer early reactions and are treated with antihistaminics and corticosteroid are less likely to develop late reactions.

Prediction of antivenom reactions

Since, Skin and conjunctival hypersensitivity tests will reveal IgE mediated Type I hypersensitivity to horse or sheep proteins. However, since majority of early (anaphylactic) or late (serum sickness type) reactions result from direct complement activation rather than from IgEmediated these tests are not predictive. Since they may delay treatment.

Neurotoxic envenoming with respiratory paralysis:

Assisted ventilation with room air or oxygen has been effective, and has been followed by complete recovery, even after periods of more than one month. Manual ventilation (ambu bag) by doctors, medical students, relatives and nurses has also been effective where no mechanical ventilator was available. Anticholinesterases should always be tried.

Haemostatic abnormalities: Strict bed rest to avoid even minor trauma; transfusion of factors and platelets. Ideally fresh frozen plasma (FFP) and cryoprecipitate or platelet concentrates or, if not available, fresh whole blood transfusions.

Intramuscular injections should be avoided.

Shock, myocardial damage: Hypovolaemia should be treated with colloids, with the observation of the central venous pressure. Ancillary pressor drugs (dopamine or epinephrine-adrenaline) may be needed. Patients with hypotension associated with bradycardia can be treated with atropine.

Acute kidney injury: Conservative treatment or dialysis.

Dark brown urine (myoglobinuria or haemoglobinuria):

Correct hypovolaemia with the help of intravenous fluids, correct acidosis with a slow intravenous infusion rate of 50-100 mmol of sodium bicarbonate similar to crush syndrome, consider a single infusion of mannitol also.

MATERIALS AND METHODS

STUDY POPULATION :

Patients with history of snake bite who fulfill the inclusion and exclusion criteria getting admitted in General Medicine wards of GOVT RAJAJI HOSPITAL, MADURAI, during the period of JANUARY 2016 TO JUNE 2016.

INCLUSION CRITERIA :

All patients with history of snake bite with signs of envenomation aged 15 to 60 years of both sexes admitted in general medicine wards of Government Rajaji Hospital, Madurai.

EXCLUSION CRITERIA :

Patients with pre existing renal diseases and ischemic heart diseases with present history of snake bite.

Patients with the risk of developing renal diseases due to underlying diseases like hypertension, diabetes, connective tissue diseases and chronic infection. Patients with history of medications (steroids, nephrotoxic drugs) within last 10 days, before the snake bite.Neurotoxic snake bites were not included

Patients referred after 3 days of snake bite.

DATA COLLECTION :

Data will be collected using a pretested proforma meeting the objectives of the study. Detailed history, physical examination, and necessary investigations will be undertaken.

The purpose of the study will be explained to the patient and informed consent obtained.

Using noninvasive methods acute kidney injury in snake bite patients who fulfill the inclusion criteria is assessed.

The analysis of the data will be done using appropriate statistical methods.

LABORATORY INVESTIGATIONS :

Complete haemogram, Whole blood clotting time, Bleeding time, Blood urea and serum creatinine, CREATINE PHOSPHO KINASE (CPK), USG abdomen and pelvis, Prothrombin time.

DESIGN OF STUDY : Prospective cross sectional study

PERIOD OF STUDY : JANUARY 2016 TO MAY 2016 (5 MONTHS)

PARTICIPANTS :

Patients admitted with history of snake bite with signs of envenomation in General Medicine wards of Government Rajaji Hospital, Madurai from January 2016 to May 2016.

METHOD :

Around 250 patients admitted to medicine department with history of snake bite with features of hemotoxicity was tested for serum CPK levels, routine blood investigations and USG abdomen and pelvis was also done to rule out chronic kidney disease.

First and third day creatinine values were measured and the patients were divided into cases and controls for intervention with sodium bicarbonate (1 ampoule in 500 ml NS over 1 hour) with serial monitoring for hypokalemia

The patients were later followed up with repeat renal function tests to assess the need for hemodialysis.

OBSERVATION AND RESULTS

AGE DISTRIBUTION OF SNAKE BITE CASES AND CONTROL

Age distribution			
No Intervention		Intervention	
n=125		n=125	
Mean ± SD	(min, max)	Mean ± SD	(min, max)
39.4 ± 14.9	(18, 68)	48.6 ± 10.0	(20, 65)

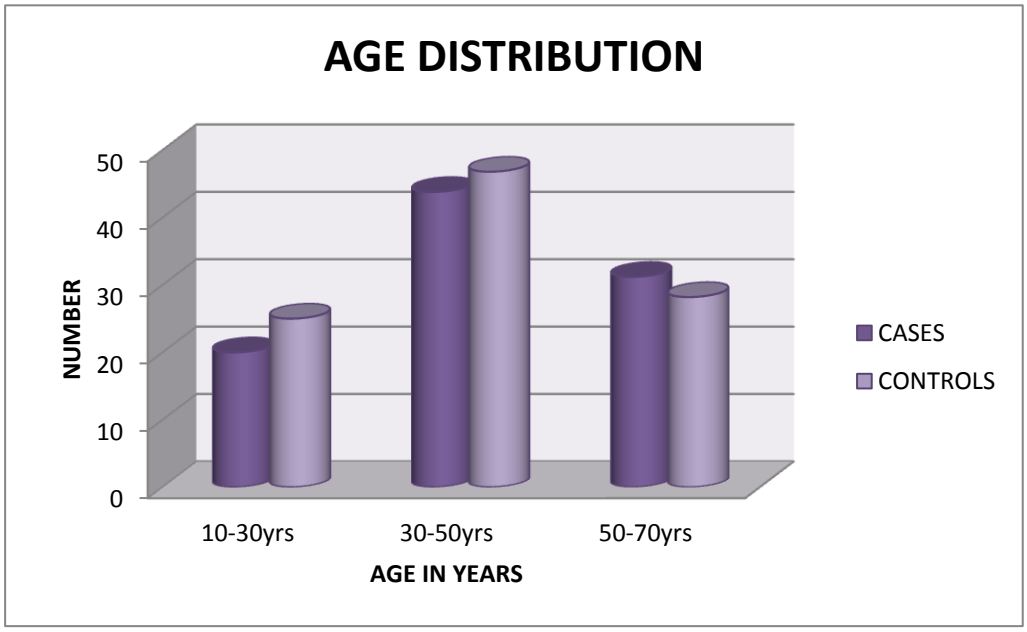
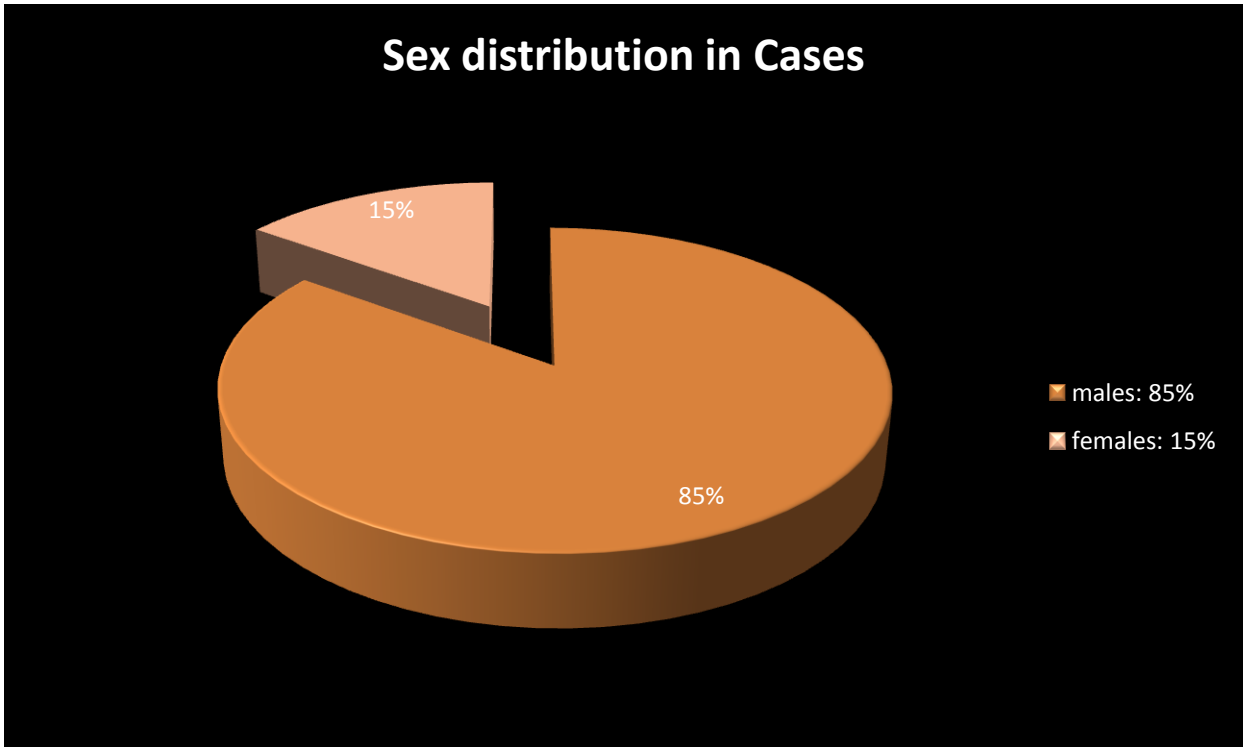


TABLE 1 :

This chart shows the maximum age distribution of cases and control is between 30-50 years of age. This carries significance since the working and productive population falls within this group.

GENDER DISTRIBUTION

Gender	Group			
	CONTROL		CASES	
	No	%	No	%
Male	96	76.8	106	84.8
Female	29	23.2	19	15.2
Total	125	100.0	125	100.0



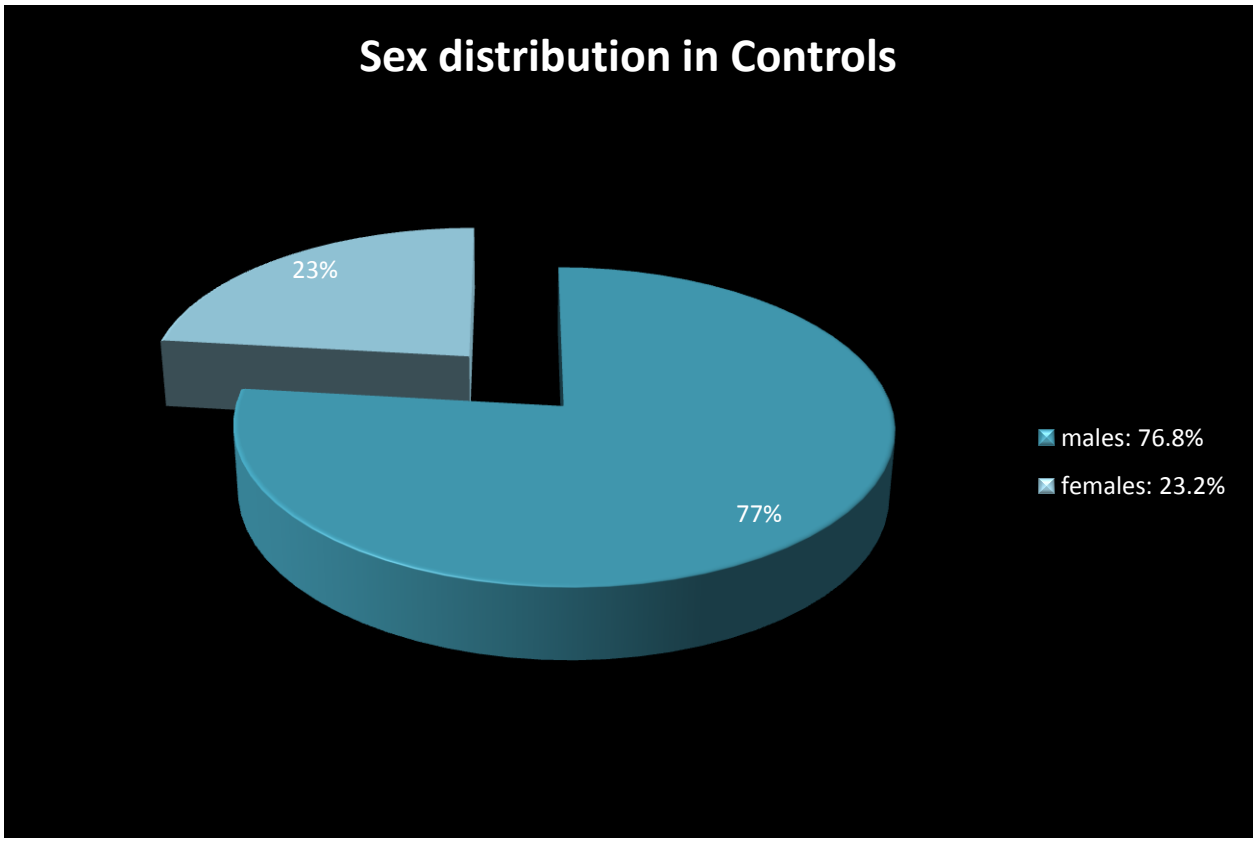


TABLE 2:

This pie diagram shows that the gender affected mostly are males. This is because they remain outdoors than females and so are affected.

	No Intervention		Intervention	
	n=125		n=125	
	Mean ± SD	(min, max)	Mean ± SD	(min, max)
CPK	344.5 ± 240.0	(38, 955)	405.8 ± 147.5	(167, 784)
p-value	0.016 (Significant)			

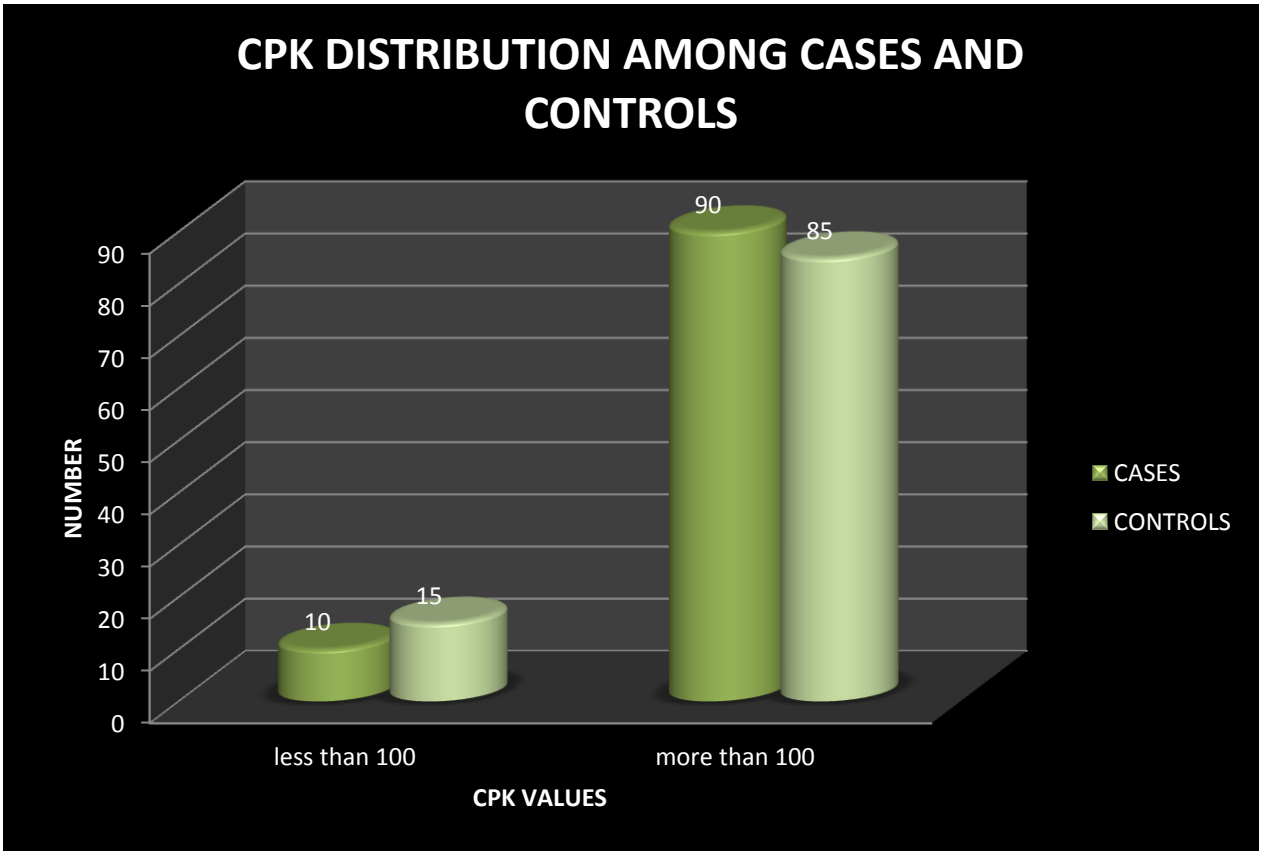


TABLE 3

This diagram shows that cases with CPK elevation were mainly included under study.

CREATININE LEVELS IN CASES AND CONTROLS

	No Intervention		Intervention	
	n=125		n=125	
	Mean ± SD	(min, max)	Mean ± SD	(min, max)
1st day - creatinine	1.2 ± 0.5	(0.5, 4.5)	0.9 ± 0.3	(0.5, 2.5)
p-value	<0.001 (Significant)			

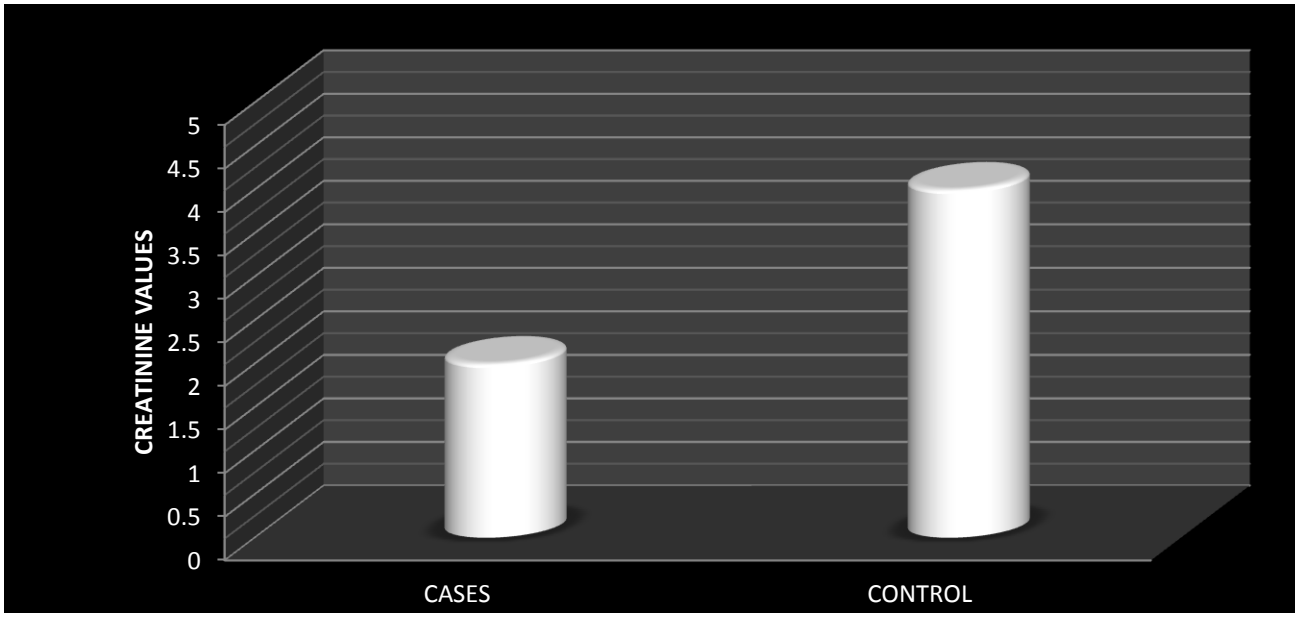


TABLE 4 :

This chart shows that there was a significant difference in creatinine values in the controls and cases group which was taken after soda bicarbonate infusion

	Group			
	No Intervention		Intervention	
	n=125		n=125	
	Mean ± SD	(min, max)	Mean ± SD	(min, max)
3rd day - Creatinine	2.4 ± 1.3	(1.0, 6.5)	2.5 ± 1.3	(0.8, 6.3)

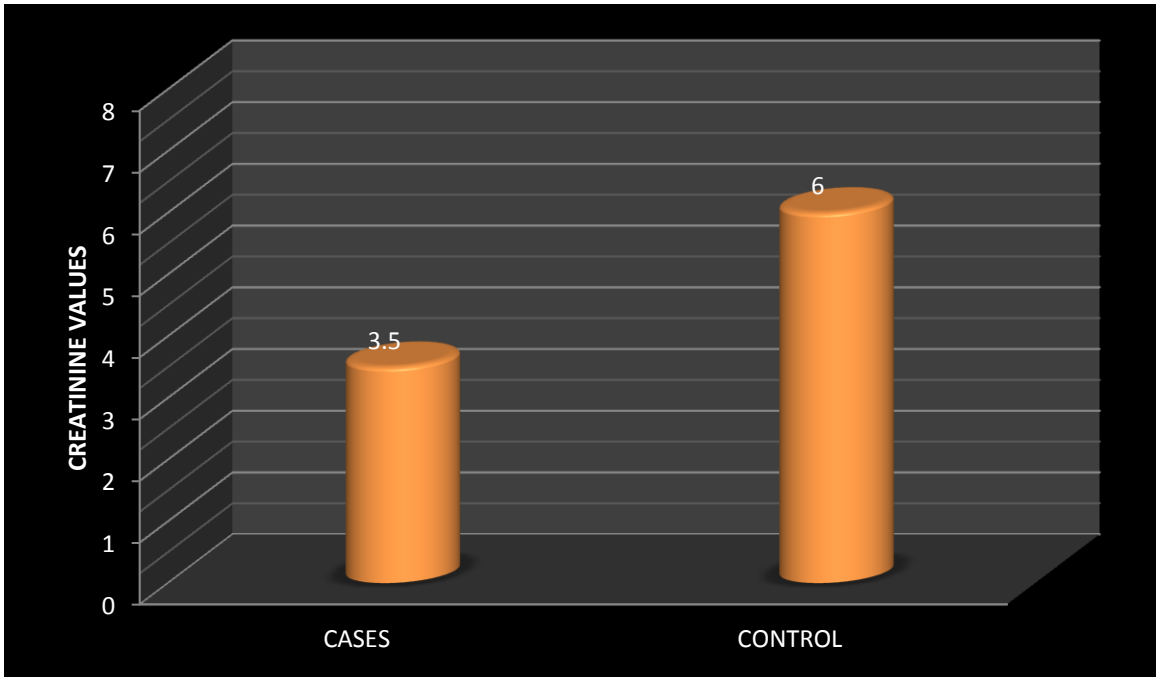


TABLE 5:

This chart shows that there was less increase in third day creatinine values in the cases group post soda bicarbonate infusion than in the control group.

HEMODIALYSIS REQUIREMENT

HD Done	Group			
	No Intervention		Intervention	
	No	%	No	%
Yes	35	28.0	15	12.0
No	90	72.0	110	88.0
Total	125	100.0	125	100.0
p-value	p=0.002 (Significant)			

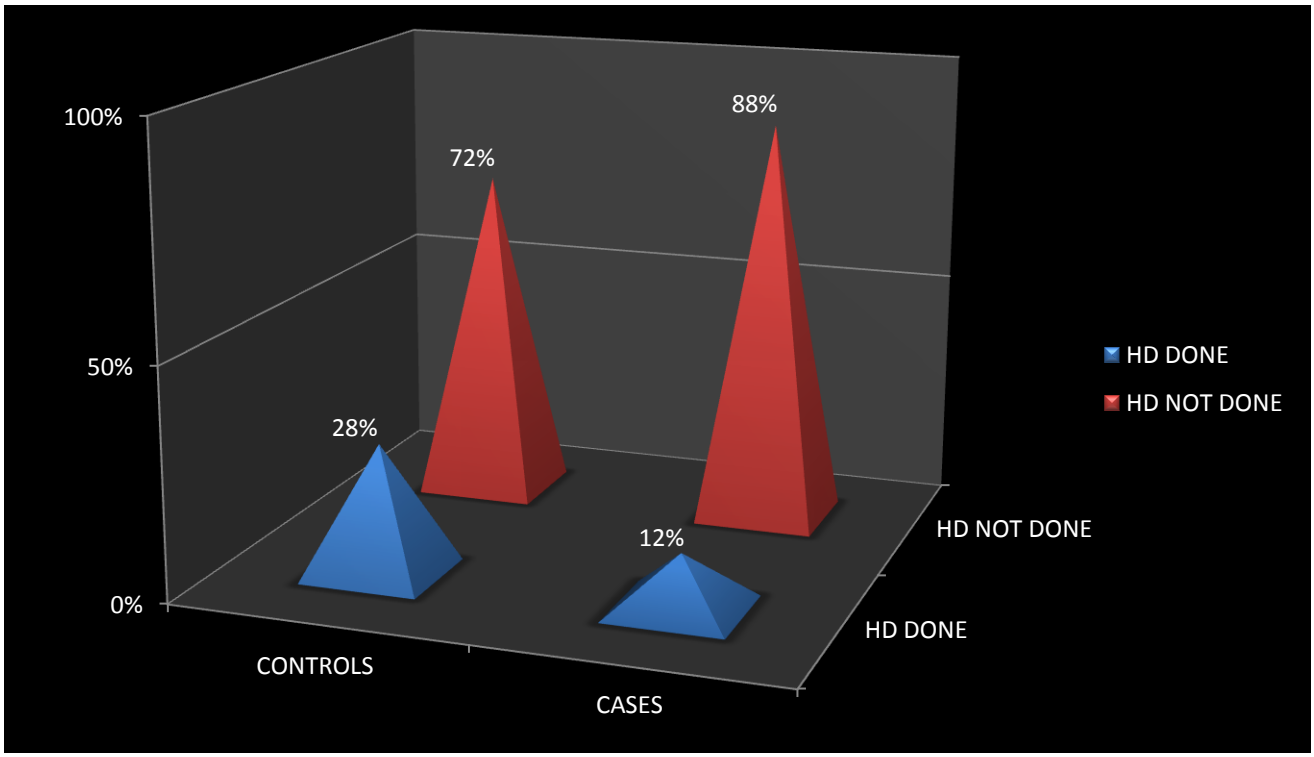


TABLE 6:

This chart shows that the requirement of hemodialysis in AKI group with significant creatinine values was less in cases than in controls with statistical significance.

DISCUSSION

In our study around 250 patients were analysed after applying inclusion and exclusion criteria, clinical examination were done for all of them. Later first and third day urea and creatinine values were done with CPK values and other routine investigations were also done.

The observations made in the study were males formed most of the study population around 75-80% and most of them were within the age group of 35-45 years with around 15% are less than or equal to 25 years, 27% are between 25-35 years of age, 31% between 35-45 years and 27 % are 45 and above years.

And it was also found out that the higher the value of CPK in these patients the more the patients go into to develop AKI. So intervention group was tried with sodium bicarbonate because one of the mechanisms attributed is precipitation of myoglobin in the distal tubules thereby leading to acute tubular necrosis.

It was found that the intervention group had much lesser incidence of dialysis requiring creatinine levels with statistical significance. Around 85% of cases recovered following soda bicarbonate infusion without dialysis whereas those without infusion only 67% recovered.

LIMITATIONS OF THE STUDY

In this study the total CPK was tested and not the iso enzyme form. So there is a possibility of non specific elevation of CPK due to other factors like MI/ angina. Other parameters of acute kidney injury like NGAL were not measured. The cases were not followed up thereafter to record for any chronic lesions developing after this snake bite.

SUMMARY

- Around 250 patients 85% were males and 15% were females with most of the males within 35-45 working population.

- Around 15% are less than or equal to 25 years, 27% are between 25-35 years of age, 31% between 35-45 years and 27 % are 45 and above years.

- More than 90% patients with cellulitis or with history of hemotoxicity developed CPK elevations of more than 150 which was significant

- First day creatinine values were higher in the non intervention group than in the intervention groups by around 45%

- Third day creatinine values were also greater in the non intervention than post soda bicarbonate infusion group.

- And 28% were requiring hemodalysis in the non-intervention group. But around 12% in the intervention group were requiring hemodialysis.

CONCLUSION

This study correlates one of the factors in the prevention of AKI, but there are more than 10 mechanims attributed to the cause of renal failure in snake bite patients. So this intervention may be in addition to the other treatment with IVF, anti-venom, antibiotics and prevention of dehydration. The CPK values tend to correlate with the incidence of renal failure and it can be prevented with soda bicarbonate infusion. Other factors like NGAL levels were not measured to asses for the incidence of renal failure. So all these is to be considered in treating a patient with hemotoxicc snake bite with elevated CPK values.

Ramalingam	55/M	70302	234	56/0.9	90/1.3	NO
Maari	33/M	70330	444	67/1.0	79/1.1	NO
Ibrahim	34/M	70335	167	69/1.8	87/2.0	NO
Karthick	31/M	70345	455	55/1.1	95/1.9	NO
Muniyammal	65/F	70445	277	59/1.0	85/1.6	NO
Duraisamy	48/M	70456	568	88/2.0	59/2.9	NO
mokkasamy	55/M	70495	377	77/0.9	86/1.9	NO
Nagaraj	49/M	1098759	257	33/0.7	93/3.7	No
Ponnathal	20/F	1098713	534	87/1.4	194/1.8	No
Arumainathan	40/M	1101972	197	25/0.5	85/1.8	No
Rajeshwari	56/M	1101172	587	43/0.9	121/ 1.5	No
Pandi	65/F	1102382	492	23/0.9	78/1.4	No
Sundar	33/M	1102241	285	35/0.9	114/5.3	Yes
sathya	25/M	48295	784	84/1.5	150/2.8	No
Rajendran	49/M	1088758	257	33/0.7	53/3.7	No
Maruthu	50/M	1088719	634	87/1.4	24/1.8	No
Mapillai rasa	60/M	1141970	297	25/0.5	88/0.8	No
Sendhoor	26/M	1102171	287	43/0.9	122/ 1.5	No
Parvathi	45/F	1109381	392	23/0.9	79/1.5	No
Selvan	33/M	1108240	585	35/0.9	124/6.3	Yes
maniapan	45/M	48796	384	84/1.5	180/1.8	No
Alagappan	59/M	1098758	257	33/0.7	53/1.9	No
Arasu	30/M	1098719	634	87/1.4	124/1.5	No
Ameean	50/M	1101970	297	25/0.5	88/1.1	No
Jafer	46/M	1101171	287	43/0.9	101/ 1.1	No
Savuriammal	55/F	1102381	392	23/0.9	79/1.3	No
Sekar	53/M	1102240	585	35/1.9	124/5.3	Yes
manikandan	55/M	48296	184	84/2.5	180/2.8	No
Masilamani	59/M	1098758	257	33/0.7	53/1.7	No
Sakarapandi	30/M	1098719	664	87/1.4	94/1.8	No
Sonai	50/M	1101970	247	25/0.5	85/1.8	No
Chinnasamy	46/M	1101171	387	43/0.9	134/1.5	No

Tamilselvan	55/F	1102381	592	23/0.9	66/1.4	No
Ganesan	53/M	1102240	685	35/0.9	99/1.1	No
pitchai	55/M	48296	284	84/1.5	80/1.8	No
Swaminathan	59/M	1098758	257	33/0.7	53/1.7	No
Innasi	30/M	1098719	634	87/1.4	74/1.5	No
Gopal	50/M	1101970	297	25/0.5	88/1.4	No
Madhan	46/M	1101171	287	43/0.9	90/ 1.5	No
Veerayi	55/F	1102381	392	23/0.9	111/1.4	No
Chandrakumar	53/M	1102240	585	35/0.9	124/2.3	No
bose	55/M	48296	384	84/1.5	180/1.8	No
Kumaravel	30/M	1098719	634	87/1.4	124/1.8	No
Gowthaman	50/M	1101970	297	25/0.5	88/2.8	No
Muthusamy	46/M	1101171	287	43/0.9	91/ 1.5	No
Annakodi	55/F	1102381	392	23/0.9	79/1.3	No
Mayilsamy	53/M	1102240	585	35/0.9	124/3.3	Yes
thavasi	55/M	48296	384	84/1.5	180/1.8	No
Iyyappan	30/M	1098719	634	87/1.4	124/3.8	No
Muniyasamy	50/M	1101970	297	25/0.5	88/1.8	No
Saamiappan	46/M	1101171	287	43/0.9	101/ 1.5	No
Saratha	55/F	1102381	392	23/0.9	79/1.4	No
Devatharsamy	53/M	1102240	585	35/0.9	124/5.3	Yes
deleipan	55/M	48296	384	84/1.5	180/2.8	No
Pradeepan	30/M	1098719	634	87/1.4	124/3.8	No
Veerasamy	50/M	1101970	297	25/0.5	88/1.8	No
Vetrimaran	46/M	1101171	287	43/0.9	101/ 1.5	No
Punithavathi	55/F	1102381	392	23/0.9	79/1.4	No
Seeman	53/M	1102240	585	35/0.9	124/5.3	Yes
sevukan	55/M	48296	384	84/1.5	180/2.8	No

Kamaraj	30/M	1098719	634	87/1.4	124/3.8	No
Madhusoothan	50/M	1101970	297	25/0.5	88/1.8	No
Vinoth	46/M	1101171	287	43/0.9	101/ 1.5	No
Suseela	55/F	1102381	392	23/0.9	79/1.4	No
Bharathan	53/M	1102240	585	35/0.9	124/5.3	Yes
mokkai	55/M	48296	384	84/1.5	180/2.8	No
Dhaneesh	30/M	1098719	634	87/1.4	124/3.8	No
Dharmaraj	50/M	1101970	297	25/0.5	88/1.8	No
Prabhakar	46/M	1101171	287	43/0.9	101/ 1.5	No
Pavalammal	55/F	1102381	392	23/0.9	79/1.4	No
Ponraj	53/M	1102240	585	35/0.9	124/5.3	Yes
kanthan	55/M	48296	384	84/1.5	180/2.8	No
Aadhith	30/M	1098719	634	87/1.4	124/3.8	No
Amirtham	50/M	1101970	297	25/0.5	88/1.8	No
Arasan	46/M	1101171	287	43/0.9	101/ 1.5	No
Devi	55/F	1102381	392	23/0.9	79/1.4	No
Dinesh	53/M	1102240	585	35/0.9	124/5.3	Yes
srithar	55/M	48296	384	84/1.5	180/2.8	No
Arunachalam	30/M	1098719	634	87/1.4	124/3.8	No
Ramesh	50/M	1101970	297	25/0.5	88/1.8	No
Sureshkumar	46/M	1101171	287	43/0.9	101/ 1.5	No
Brindha	55/F	1102381	392	23/0.9	79/1.4	No
Ahamed	53/M	1102240	585	35/0.9	124/5.3	Yes
dhanush	55/M	48296	384	84/1.5	180/2.8	No
Thirunavukarasu	30/M	1098719	634	87/1.4	124/3.8	No

Sathyarengan	50/M	1101970	297	25/0.5	88/1.8	No
Shanmuganathan	46/M	1101171	287	43/0.9	101/ 1.5	No
Sakunthala	55/F	1102381	392	23/0.9	79/1.4	No
Kannan	53/M	1102240	585	35/0.9	124/5.3	Yes
balamurugu	55/M	48296	384	84/1.5	180/2.8	No
Krishnan	30/M	1098719	634	87/1.4	124/3.8	No
Vathsalyan	50/M	1101970	297	25/0.5	88/1.8	No
Anil thomas	46/M	1101171	287	43/0.9	101/ 1.5	No
Chellam	55/F	1102381	392	23/0.9	79/1.4	No
Marthandan	53/M	1102240	585	35/0.9	124/5.3	Yes
masilamani	55/M	48296	384	84/1.5	180/2.8	No
Jegan	30/M	1098719	634	87/1.4	124/3.8	No
Maaran	50/M	1101970	297	25/0.5	88/1.8	No
David	46/M	1101171	287	43/0.9	101/ 1.5	No
Meenakshi	55/F	1102381	392	23/0.9	79/1.4	No
Paapan	53/M	1102240	585	35/0.9	124/5.3	Yes
hebran	55/M	48296	384	84/1.5	180/2.8	No
Sheikh	30/M	1098719	634	87/1.4	124/3.8	No
Abdullah	50/M	1101970	297	25/0.5	88/1.8	No
Ragunathan	46/M	1101171	287	43/0.9	101/ 1.5	No
Siva	55/F	1102381	392	23/0.9	79/1.4	No
ajith	53/M	1102240	585	35/0.9	124/5.3	Yes
alagu	55/M	48296	384	84/1.5	180/2.8	No
Mahendran	30/M	1098719	634	87/1.4	124/3.8	No
Malaiarasan	50/M	1101970	297	25/0.5	88/1.8	No
Paraman	46/M	1101171	287	43/0.9	101/ 1.5	No
Chidambaram	55/F	1102381	392	23/0.9	79/1.4	No
Narendhran	53/M	1102240	585	35/0.9	124/5.3	Yes

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Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.Kirthika. K.
Course	:	PG in MD., General Medicine
Period of Study	:	2015 - 2018
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A study to correlate elevated creatine phosphor kinase levels with snake bite and acute kidney injury
Ethical Committee as on	:	26.10.2016

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

DEAN
Madurai Medical College
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