A Dissertation

On

A STUDY OF ACUTE RENAL FAILURE DUE TO SNAKE BITE ENVENOMATION

GOVERNMENT MOHAN KUMARAMANGALAM MEDICAL COLLEGE

MD GENERAL MEDICINE

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

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DECLARATION

I hereby declare that the dissertation titled **"A STUDY OF ACUTE RENAL FAILURE DUE TO SNAKE BITE ENVENOMATION"** was done by me in Government Mohan Kumaramangalam Medical College Hospital, Salem during the period of my post graduate study for **M.D.,** Branch – I, General Medicine from 2003 – 2006.

This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of the University regulations for the award of M.D. Degree in General Medicine.

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CERTIFICATE

This is to certify that the dissertation titled **" A STUDY OF ACUTE RENAL FAILURE DUE TO SNAKE BITE ENVENOMATION"** is the original work done by **Dr.R.KARTHIKEYAN**, Post Graduate student in the Government Mohan Kumaramangalam Medical College, Salem – 636 030, in partial fulfillment of the university rules and regulations for the award of **M.D. Degree Branch – I,** General Medicine, under my guidance and supervision during the academic period from 2003 – 2006.

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CONTENTS

INTRODUCTION

Snakes are a fascinating part of nature. Their colour, movement, and secretive habits make them more mysterious. There are about 2700 species of snakes recognized world over of which about 450 species are venomous..

Venomous snakes are broadly classified into 4 families : Elapidae, Viperidae, Hydrophilidae, Colubridae. Snakes are classified on morphological grounds from the arrangement of their scales (Lepidosis), dentition, Osteology, Myology, Sensory Organs and Hemipenis and more recently by immunological studies of their venoms and serum proteins.

All medically important species of snakes have one or more pairs of enlarged teeth, the ‘ fangs ’ in the upper jaw by which venom is introduced through the skin of human victim.

ARF has been mostly reported following bites by snakes of first three of these families, with the majority following viper bites (Chugh ET AL. 1984, 1989). Snakes whose bites are known to cause renal failure include the sea-snake, Russell’s viper, saw-scaled viper, puff adder, rattlesnake, tiger snake, green pit viper, Bothrops jararaca boomslang, gwardar, dugite, and Cryptophis nigrescens.

Information on the precise incidence of snake-bite-induced ARF in different geographical regions is lacking. The incidence following Saw scaled viper or Russells’s viper bites in India varies from 13 to 32 percent (Chug et al.1984). The reported incidence from other countries varies between 1 and 27 percent.

The clinical manifestations depend upon the dose of venom injected ; and vary from mild local symptoms to extensive systemic manifestations. Pain and swelling of the bitten part appear within a few minutes and may be followed by blister formation and ecchymosis. Bleeding is seen in 65percent of cases and manifests as continuous ooze from the site of the bite, haematemesis, malena, and haematuria. Bleeding can also occur into the muscles and serosal cavities, and may be severe enough to produce shock. The blood is incoagulable in patients with severe systemic envenomation. Sea-snake bites cause myonecrosis, resulting in severe muscle pains and weakness.

The first indication of renal failure is oliguria or anuria, which develops within a few hours to as late as 96 h after the bite (Chuge et al. 1984). About half the cases give a history of passage of 'cola-coloured' urine. Non-oliguric renal failure is seen in less than 10percent of cases. Patients with severe bleeding, disseminated intravascular coagulation or secondary sepsis may present with hypotension. Life-threatening hyperkalemia necessitating immediate dialysis may develop in those with intravascular haemolysis. Oliguria usually lasts for 4-15 days, and its persistence indicates the possibility of acute cortical necrosis(Chugh 1989).

Laboratory investigations show evidence of coagulopathy, there is severe hypofibrinogenaemia, reduction of factors V, X, and XIIIA, protein C, and antithrombin C, depletion of factor V, X and fibrinogen and elevation of fibrin degradation products are frequently observed. Leukocytosis and elevated haematocrit due to haemoconcentration may also be seen.

Eventhough the basic therapeutic approach to renal failure following snake bite is the same as that for ARF due to any other cause, problems such as bleeding, shock, and sepsis complicate management. Early administration of antivenom is vital in patients with systemic envenomation. Experimental studies have shown that delay in administration results in a steep increase in the antivenom dose requirements indications include incoagulable blood, spontaneous systemic bleeding, intra vascular haemolysis, local swelling involving more than 2 segments of the bitten limb, and a serum FDP concentration greater than 80 µg/ml in those reporting within 2h of the bite (Warrell 1989, 1999). Knowledge of the offending snake species allows administration of monovalent antivenom wherever this is available. Immuno diagnostic techniques are helpful in the easy and rapid identification of the venom antigen. ELISA has been used extensively in the rural Thailand, but the currently available test is not quick enough for the clinicians. Precise identification of the snake is not essential for management in regions where only polyvalent antivenom is available. Indian authorites recommend until the effects of systemic envenomation disappear (Tariang ET AL.1999). A simple way is to monitor efficacy is by monitoring whole blood clotting time three to four times a day. Coagulability is generally restored within 6 h of an adequate dose. The clotting time must be done for at least 3 more days, as delayed absorption of the venom could lead to recurrence of the coagulopathy. Immunoassays permit serial estimation of venom levels, and are usefull in guiding antivenom therapy. In sea – snake envenomation, patients require from 100 to 1000 units of Enhydrina schistose

antivenom. Other therapeutic measures include rerpalcement of blood loss with fresh blood or plasma, maintenance of electrolyte balance, administration of tetanus immunoglobulin, and treatment of pyogenic infection with antibiotics. The overall mortality rate is about 30 percent (Chug ET AL. 1984).

The kidneys are normal or slightly enlarged, and the surface may show petechial haemorrhages. Light microscopy shows acute tubular necrosis in 70-80 percent of patients (Chugh 1989). The tubules are lined by flattened epithelium and the lumina contain desquamated cells and hyaline or pigment casts. Varying degrees of interstitial oedema, inflammatory cell infiltration with eosinophils, mast cells and hyperplastic fibroblasts, and scattered areas of haemorrhage may be seen. Electron microscopy reveals dense intracytoplasmic bodies representing degenerated organelles in the proximal tubules, and electron-dense mesangial deposits. Acute interstitial nephritis necrotizing vasculitis involving interlobular arteries, and crescentic glomerulonephritis may be seen occasionally (Sitprija et al. 1982). Acute cortical necrosis (Fig 7) carries the worst prognosis and is seen in about 20 – 25 percent of ARF cases following Russell's viper and E. carinatus bites(Chug ET AL. 1984).

A number of clinical and experimental studies have provided insights into the pathogenetic mechanisms that lead to ARF in snake-bitten patients. These include direct nephrotoxicity of venom, hypovolaemia, haemolysis, myoglobinuria, and disseminated intravascular coagulation.

Renal lesions can develop as a result of direct cytotoxic effects of the snake venom on the kidney. Rats injected with the venoms of B.Jararaca, Agkistrodon piscivorus and rattlesnake developed increased excretion of tubular enzymes and histopathological changes of acute tubular necrosis (Burdmann et al.1983). Administration of Russell's viper venom leads to a dose- dependent decrease in inulin clearance in the isolated perfused rat kidney. Willinger et al.(1995) showed extensive destruction of the glomerular filter lysis of vessel wall, and epithelial cell injury in all segments of the tubule following administration of Russell's viper venom to experimental animal. The structure of some of the snake venoms, including the saparatoxin of the Israeli burrowing wasp, is similar to endothelin – I, one of the most potent vasoconstrictor substances known. Vasculotoxic factors have been isolated from the venoms of several snakes, including E.carinatus, Vipera palastinae, Agkistrodon halys, B. Jararaca, and Habu snake. Studies using the Habu snake venom have shown development of mesangiolysis.

Hypotension and circulatory secondary to bleeding and release of kinins and depression of the medullary vasomotor center or the myocardium play a significant pathogenetic role. Kinin-forming enzymes (kininogenases) are present in crotalid venom, V. oakastubae deoresses the medullary vasomotor center, and Bitis arientans venom causes hypotension through a combination of myocardial depression, arteriolar dilatation, and increased vascular permeability.

Severe haemolysis has been observed following bites by Russell's viper and E. carinatus bites in humans and experimental animals. The haemolysis results from the action of phospholipase A_2 , forms 70 percent of the venom content of Russells's viper and acts on plasma lecithin, leading to the production of haemolytic lysolecithin. Microangiopathic haemolytic anaemia has been recorded following Agkistrodon rhodostoma, Russell's viper, puff adder, and gwardar bites. Bites by sea-snakes produce severe muscle necrosis and the resulting myoglobinuria, especially in the presence of other factors such as dehydration and acidosis, can give rise to ARF.

Disseminated intravascular coagulation has been observed in experimental animals as well as in patients bitten by viper snakes. Infusion of Russell's viper or E.carinatus venom into rhesus monkeys leads to disseminated intravascular coagulation(Chug 1989). The procoagulant factors in the venom activate factors V and X, and the subsequent activation of the coagulation cascade leads to rapid thrombin formation.

The fibrinolytic activity is either due to direct action of the venom or a physiological response to fibrin deposition. Phospholipase A2 also leads to platelet aggregation. The demonstration of fibrin thrombi in the renal microvasculature, both in clinical and experimental studies, confirms the role of disseminated intravascular coagulation in the genesis of renal lesions (Chug et al.1984).

Snake bite is an important cause of hospital admission and mortality in tropical countries like India due to occupational hazard. (Eg. Agriculture) An estimated 15,000 – 20,000 people die each year from snake bite due to its complications like ARF, DIVC etc. (Oxford text book 5th edition 2005). Incidence of ARF following viper bites ranges 10 – 30% (Chugh et al) Most important of this it is an preventable cause of ARF in India . Hence several studies sprout regarding ARF and snake bite envenomation

REVIEW OF LITERATURE

Medically important venomous Snakes

ELAPIDAE	-	Cobra
		Kraits
		Mambas
		Coral Snakes
VIPERIDAE	-	Russel Viper
		Sawscaled Viper
		Puff adder
		Pit vipers
		Rattle Snakes
		Others species

HYDROPHILIDAE	-	Enhydrina schistosa
		Hydrophis cyanacinatus
		Lapenis hardvicki
		Pelanix platinus
		Australian land snakes
COLUBRIDAE	-	Boomslang
		Bird Snake

GENERAL FEATURES OF SNAKES

Snake bite is a quick coordinated act of positioning of head, opening of mouth attacking by a forward thrust of body and head piercing the skin of victim by fangs and injecting the venom while the wound is deepened by the contraction of temporalis muscle. This active act occurs within seconds.

Snakes are present even in altitudes of 2500m. 3 African and 1 Asian (Spiting Cobras) can eject their venom from tip of the fangs as a fine spray for a distance of few meters into eyes of enemy. Venom glands are behind the eyes surrounded by compressor muscles. A duct connects it to the fangs. The scales are very ill defined in primitive snakes and distinctive in poisonous snakes such as Cobra, vipers. A very thin covering the scales is cast off periodically.

The mobile fang of viper is usually curved in and becomes erect before striking Accidental envenomation from a dead snake has been reported from the fangs by hooking and making it erect because of spasm. Protruding tongue in a close mouth through a notch in lower jaw is a sense organ to locate and get information about prey. When prey or aggressor is close by the tongue moves in and out very frequently but stops when above to strike.

Snakes are considered to have a very narrow tubular vision. They are able to locate moving objects better than stationary ones and explains the dancing of a cobra to movement of a snake charmer playing the gourd moving back and forth. Actually the snake is taking an aim to strike rather than dancing to tune.

In "PITS" viper the temperature difference as small as 1.02^0C could be detected by this very specialized pit "ELAPIDAE" inject venom by groove in the fangs while viperidae do so through tiny holes at the tip of fangs.

Characteristic points of snakes as follows :-

I. ELAPIDAE :

Body of Elapidae is long and cylindrical. Head is nearly as same width as that of neck . Pupils are rounded fangs are short fixed and grooved show they cannot penetrate clothing .

1. **COBRA :**

1.5 to 2 meters long , black in colour, head bears a hood with aspectacle mark. In absence of hood Cobra can be identified by 2 to 3 series of very dark belly scales under and below the neck or by the divided tips scales. Found in populated areas.

2. **KING COBRA :**

2.5 to 4.5 meters long. Young tiny Cobra is jet black in colour and adult ones are yellow, green, brown or black with white or yellow cross bands in body. It has a hood but no spectacle mark. Tail scales are full proximally but divided. Seen in jungles.

3. **COMMON KRAIT**

1 to 1.5 meters long, glistening black with a single or double white arches in the back beginning some distance from hood, central row of hexagonal scales on the back and creamy white belly or features. Tail scales are entire. They are seen in houses.

4. **BRANDED KRAIT**

2 meters long , alternate black and yellow bands are seen across its back.

II. VIPERIDAE

The body measures short with narrow neck. Head is triangular in shape and covered by small scales. Pupils are vertical in shape. Fangs are long, mobile and grooved, so they cannot penetrate clothing.

1. RUSSEL'S VIPERS :

Measures 1.5 meters long. Usually brown or buff coloured. There 3 rows of black diamond shape spot seen on the back. Narrow tortuous tail which has divided scales are seen . Head this short triangular shaped with distinct 'V' mark apex pointing forward is seen. Nostrils are bigger than other snakes. Belly is white with broad scales . Seen in planes.

2. SAW SCALED VIPERS :

50 to 75 Cms long , brownish gray or greenish in colour, triangular hood with a white mark on it resembling an arrow. Wavy line on each flank with diamond shaped areas between upper curves of the two wavy lines are seen . Scales on the head and body are small and coarse like a saw teeth. Tail scales are not divided.

3. **SEA SNAKES :**

Small head with flat tail. Nostril is seen at tip of snout valve. Belly Plates are broad, dull and trabeculated scales in the back. They have small fixed fangs extending posteriorly .

IDENTIFICATION OF POISONOUS SNAKES

Sl.No	Features	Poisonous	Non – Poisonous
1.	Belly scale	Large and cover entire breadth of belly.	Small or Moderately large but do not cover the entire breadth of belly.
2.	Head Scales	Small in viper may be large with a pit between the eye and nostril(pit viper), 3rd labial touching the eye and nasal shields (Cobra). Central row of scales on back enlarged and under surface of mouth with only four infra labials, the fourth being the largest (Krait)	Larger
3.	Fang	Long and Grooved	Small and solid (Un Grooved)
4.	Tail	Compressed	Not markedly compressed
5.	Habit	Generally Nocturnal	Any time

6.	Fang Mark	Two Marks with or without other teeth marks	Number of small teeth marks in a row.

VENOM AND THEIR EFFECTS :

Venom produced by snakes is considered to be are of complex toxins, produced by plants and animals. The effect of snake venom of particular species varies from animal to animal, place to place, age of snake, time of the year. The higher the altitude and low the temperature the less toxic the venom. Though venom is found to be more viscial in summer, bites in November, December and January due to unknown reasons have increased mortality and morbidity. (Oxford text book of clinical nephrology 1997)

Venom is made of enzymes, Peptides, Poly Peptides, Elements such as Zinc and Magnesium have been separated from venom. It has been shown that in vitro effect of venom may not be seen in vivo.

The venom of snake has upto to 26 enzymes with at least 10 of them in each venom. Some of the proteolytic enzymes are Arginine , Hydrolase, Collagenases, Hyaluronidase which act as a spreading factor of venom in to tissues. Phospholipase which causes hemolysis. Acetylcholine. esterase seen in cobra venom may be a factor in neuroparalytic symptoms etc. Polypeptides of low molecular weight do not have enzymatic action.

COBRA VENOM :

Neurotoxin,

Haemolysin,

Cardiotoxin,

Cholinesterases,

Nucleotidase,

Potent inhibitor of Cytochromeoxidase.

VIPER VENOM :

Hyaluronidase,

Haemolysin,

Haemorrhagin I and II.

Several enzymes and

phospholipase.

ENZYMATIC COMPONENTS IN SNAKE VENOM

Sl.No	Enzymes	Actions
1.	Acetylcholine Esterase	Catalysis and Hydrolysis of Acetylcholine
2.	Arginine Ester Hydrolase	Bradykinin release, Interference with clotting
3.	Hyaluronidase A	Reduction of Collagen Viscosity
4.	Phospholipase A	Un coupling of Oxidative Phosphorylation
5.	Phospholipase B	Hydrolysis of lisophosphatides
6.	Phosphodiesterase	Inhibitors of DNA, RNA Arabinose derivatives
7.	5'Nucleotidase	Specific Hydrolysis of Po4 Monoesterase which links with 5'position of DNA, RNA
8.	L Amino acid Oxidase	Catalysis of Amino Acids.
9.	Thrombin like enzymes	Depression of fibrinogen levels
10.	Proteolytic enzymes	Tissue destruction and bleeding
11.	Collagenases	Collagen restriction

NON ENZYMATIC COMPONENTS IN SNAKE VENOM

Sl.No	Components	Effects
1.	Neurotoxin	Post Synaptic non depolarising
2.	Cobra toxin Erabutoxin Alpha burgaratoxin	Neuromuscular Blockage of long duration, acting only on nicotinic acetyl choline receptors. To some extent cardiotoxic, Haemotoxic, anticoagulant
3.	Cerulotoxin Beta Burgara toxin	Similar Post Synaptic Block but without binding to receptors. Presynaptic motornerve blockade.
4.	Haemorrhagins (HR – 1, HR –2) Viperidie, Crotalidae.	Direct disruption of vessel endothelium.

Procoagulant effects :

Factor IX activation by cleavage of peptide bond in factor IX by Russels, factor X activation by calcium binding to gamma glutaminic residues in X with rapid change of Xa direct prothrombin activation by clevage of peptide bonds by venom, producing an intermediate which quickly converts to thrombin, prolonged defibrination even without thrombocytopenia in E.carintus bites.

Anticoagulant effects :

Inhibition of platelet aggregation, inhibition of clotting factors (or) their activation, direct fibrinolysis (or) fibrinogenolysis (or) by direct action on plasminogen (or) its proactivator.

Zinc, Mettaloprotein in saw

Scaled viper - Prothrombin fibrinogen binding mechanism.

Cardiotoxin - Neuromuscular blockade, Hemolysis, Cytotoxicity, Cardiac arrest.

The Cobra venom components are small molecular weight substances which are absorbed rapidly into blood where as viper toxins are larger molecular weight substances which are absorbed through lymphatics and have slower onset of action.

The 3 dimensional structure of venom suggest that neurotoxins have a central core and three loops. The toxicity is due to Aminoacid Sequences. 30-40 present in second loops. It is said that 15 drops of viper venom or 3 drops of cobra venom is fatal to all adult men and 1 drop of sea snake venom can kill 5 men (reid)[9].

SNAKE	LETHAL DOSE
Cobra	0.12gm
Russel viper	0.15gm
Krait	0.06gm
Saw scaled viper	0.15gm

PATHOGENISIS & CLINICAL MANIFESTATIONS

1. NEUROTOXICITY

Prominent in elapid bites. Symptoms with in few minutes to 4 to 6 hours. The effect of neurotoxins is strictly at peripheral level only on neuromuscular junction blocking the Acetylcholine receptors or in muscle itself. Muscles supplied by cranial nerves are first affected resulting in ptosis, paralysis, cyanosis, convulsions, coma and death. Symptoms are totally reversed if treated early.

2. CYTOTOXICITY

Tissue edema, bullae, necrosis, ulceration caused by viper & some cobra bites are due to cytotoxic components of venom. Haemolysis cause redcells lysis, leukolysis, causes leucocyte lysis, haemorrhagin causes vascular endothelial damage, cytolysins cause damage to internal organs such as liver, kidney, myocardial tissues etc. Rhabdomyolysin in sea snakes venom causes extensive necrosis of striated muscles, which can lead to myoglobinuria, and renal failure.

The protease, Hyaluronidase and release of endogenous histamine, 5 HD causes local reaction, inflammation, and necrosis.

3. CARDIOTOXICITY

Seen in poisoning of puff adder, pit viper, diamond back rattle snake. Patients have cardiac rhythm abnormalities, myocarditis, hypotension which can result in death.

4. MYOTOXICITY

Seen in sea snakes venomation. Severe pain of muscles of extremities, trunk and neck occurs. Muscle necrosis lead to myoglobinuria and hyperkalemia leading to renal failure and cardiac arrest.

5. HAEMOTOXICITY

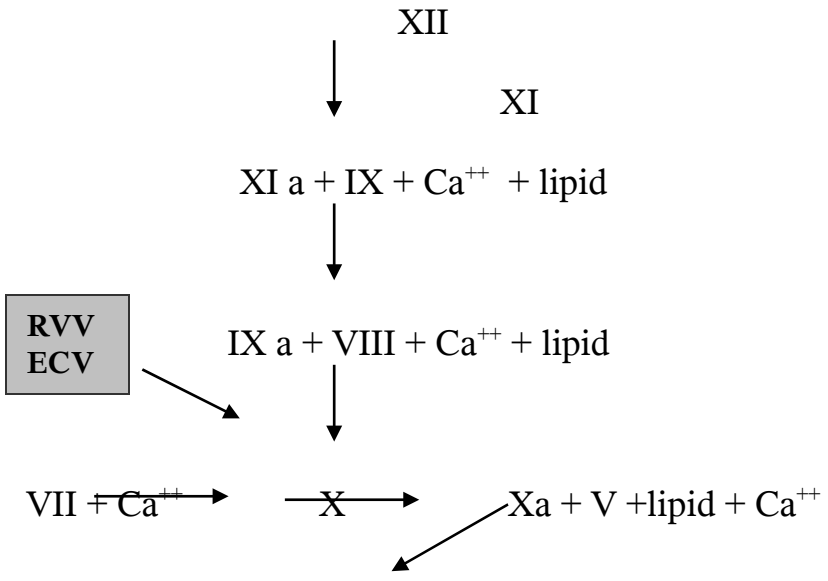
Bleeding, haemolysin and abnormal coagulation. The most striking abnormality following viper bites are bleeding and coagulation defect. It depends on procoagulant,

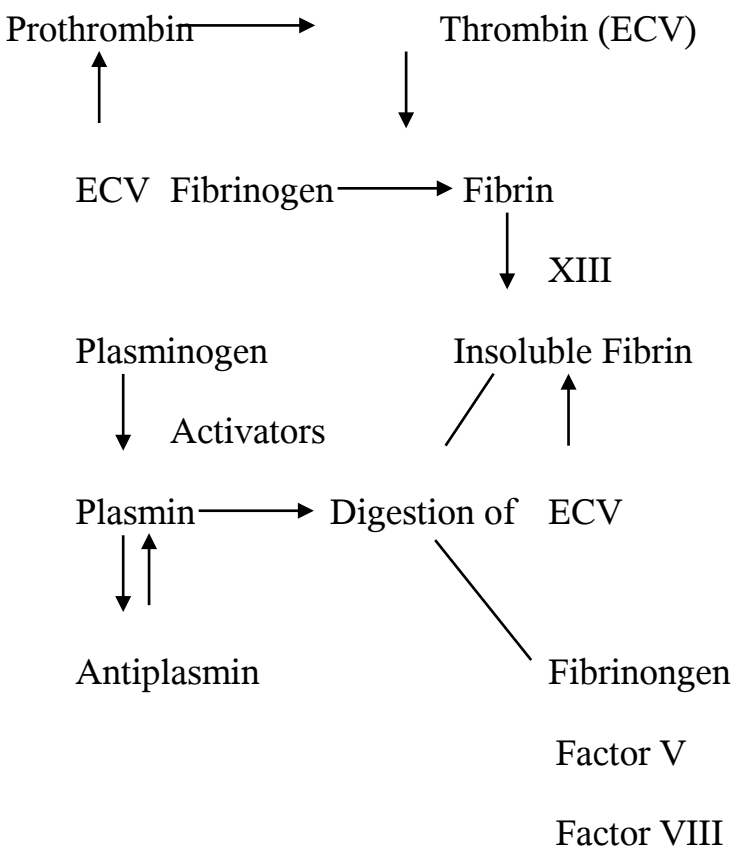
anticoagulant, fibrinolytic component of injected venom. Direct activation of prothrombin has been observed in venoms of elapidae, viperidae, colubridae.

If the venom dose is large, massive intravascular clotting occurs which can stop the circulation and cause rapid death. With smaller doses of venom there is continuous inactivation of fibrinogen producing a fragile fibrin more susceptible to lysis. Russels viper venom selectively activate factor X . Echis carinatus venom besides activation of factor X also accelerates conversion of prothrombin to an abnormal thrombin. This abnormal thrombin promotes coagulation but it simultaneously prevents stabilization of fibrin both by inhibiting factor XIII and stimulating plasminogen activity.

In viper bites although shock and hemorrhage usually resolved within a week the coagulation changes can continue for 2 weeks or longer.

Site of Action of snake venom on coagulation cascade.





ECV – Echis Carinatus
RVV – Russel Viper

RENAL TOXICITY

Common following Russel viper and is a major cause of death. Most snake venom are concentrated and excreted through kidney. It appears to be a direct toxicity to kidney.

Nephrotoxicity can occur due to various causes :

1. Hypovolemia

This due to vomiting , decreased fluid intake, increased capillary permeability resulting in capillary leak syndrome with intravascular syndrome. Haemorrhage can also cause Hypovolemia.

2. Hypotension

Besides factors contributing to Hypovolemia, Vasodilatation due to bradykinin release and myocarditis due to direct action of venom.

3. Hemolysis with Hemoglobinuria

Can lead to renal failure in setting of acidosis and Hypovolemia

4. Coagulation abnormalilty

Can produce DIVC which can cause haemorrhage, Hypovolemia, thrombi in microvasculature and glomerulo capillaries and microangiopathic hemolytic anemia . All these can lead to renal failure.

5. Myoglobinuria

After sea snake envenomation due to rhabdomyolysis, myoglobinuria occurs which again leads to renal failure.

Other causes of nephrotoxicity are glomerulonephritis, direct nephrotoxicity of venom, tubulo interstial nephritis and rarely papillary necrosis.

Immune complex nephritis can occur after a week due to deposition of Immune complex in glomeruli.

Acute tubular necrosis due to snake bite accounts for 70 to 80% cases. Acute cortical necrosis accounts for 20 to 30% cases. Oliguria which persist for 4 to 15 days possibility of acute cortical necrosis should be thought of. Acute cortical necrosis carries a worse prognosis. (Oxford text book 2005).

Acute Cortical Necrosis

Acute renal cortical necrosis is the most catastrophic of all types of ARF with improvement to medical care, this entity has virtually disappeared from the western world In India, the incidence of ACN in patients dialyzed for ARF has also declined from 7.1 percent in 1983 to 3 .8 percent in 1994.[24,77] In the large series reported from India, obstetrical causes accounted for ACN in 56 percent of patients. Other causes included snakebites (14.2%), hemolytic uremic syndrome (11.5%), allograft rejection (5.3%) and gastroenteritis (4.4%).

This condition should be suspected in patient with any of the above presdisposing condition and a prolonged period of oligo – anuria. The oligo – anuric phase may extend for weeks to months, and patients with diffuse cortical necrosis may never enter a diuretic phase. Recovery of renal function, if any, is extremely slow and depends upon the amount of viable cortical tissue.

In our study 1 patient recovered as it was Patchy cortical necrosis. If it has been the case of diffuse cortical necrosis the prognosis would be poor. Even in patients who achieve a partial functional recovery, the renal function invariably deteriorates with the passage of time and ultimately culminates in end stage renal disease.

The gold standard for establishing the diagnosis has been renal histology shows variable degree of necrosis off all elements of renal parenchyma, especially in the cortical region. A small amount of cortical tissue in the sub capsular and juxtamedullary region may be spared in patients with diffuse ACN. Detection of cortical tram – track or eggshell calcification on plain X- ray of abdomen or ultrasonography is helpful but is seen in only a minority . In recent years. CT scan has emerged as a good non – invasive imaging modality for early diagnosis of ACN [78,79].

The characteristic finding is the presence of a hypo attenuating sub capsular rim of renal cortex following contrast injection. In addition, a non-contrast CT scan is more sensitive in picking up the cortical classification. It must be emphasized that a needle biopsy can miss a patchy cortical necrosis and presence of a 'diffuse' ACN on biopsy could overestimate the extent of lesions because of sampling error.

Therefore, it is important to take the clinical course of the patient into consideration before deciding on the probability of reversibility or otherwise of the renal failure. A prolonged period of dialytic support while waiting for any evidence of renal functional recovery should therefore be attempted in all patients.

TABLE 1: HISTOPATHOLOGICAL CHANGES IN CASES OF SNAKE BITE

	Autopsy	Biopsy	Total	%
Glomerular Changes	6	4	10	4.3
Cortical Necrosis	14	11	25	60.9
Ballooning of capillaries	8	5	13	31.7
Endothelial Swelling	10	6	16	39.0
Splitting of GBM	8	3	11	26.8
Mesangiolysis	6	1	7	17.7
Capillary Thrombi	2	3	5	12.1
Mild Mesangial Proliferation	9	13	22	53.6
Tubulointerstitial Changes	-	6	6	14.8
Tubular Necrosis	-	5	5	12.1
Tubular Regeneration	2	-	2	4.8
Tubular Degeneration	-	-	-	-
Haemorrhagic interstitial Nephritis	-	-	-	-

FACTORS PREDISPOSING TO NEPHROTOXICITY

Hypovolemia,

Hypotension,

DIVC,

Myoglobinuria,

Glomerulonephritis,

Tubulo interstial nephritis,

Direct toxicity of venom.

NEPHROTOXICITY

7. ALLERGIC MANIFESTATIONS

Angioneurotic edema, abdominal pain, vomiting. Diarrhoea, Can occur due to venom, sudden collapse and hypotension can occur due to vasodilator substances in venom and endogenous histamine, serotonin release . Endogenous vasodilators cause early transcient hypotension.

CLINICAL FEATURES

Few factors modify the clinical features :

1. AGE :

Children are more seriously injured because venom dose per body mass is more than adults. Children have less protein to bind venom and smaller

extracellular volume. These factors cause rapid rise and greater plasma concentration of venom in children.

2. LOCATION OF BITE :

Bites over corpus cause more severe envenomation

2. SIZE OF SNAKE

3. VENOM GLANDS

Empty Venom Glands following recent strike elsewhere.

4. FANGS :

Broken while biting indicates severe injury.

5. EFFICACY OF FIRST AID

6. **THERMAL VISUALISATION**

Some snakes have the ability to identify a small thermal target and can deliver an accurate venom dosage. The large size of adult seems to confuse the snake resulting and unpredictable venom delivery.

SIGNS AND SYMPTOMS

Fear and anxiety are common symptoms . Dizziness and faint feeling, nausea, vomiting, abdominal pain are very common.

LOCAL AREA OF BITE :

Local pain is very common. Severity depends on extent of systemic envenomation. Swelling at site of bite is typical of poisonous snake. It can occur within 15 minutes of bite and progress to enormous size within 72 hours due to direct cytotoxic effect. Swelling and blisters seen in cobra and viper bites. Local swelling in Elapidae causes less pain but leads to coagulation necrosis. Although swelling may be due to envenomation based on which definite treatment can be initiated. It can also be due to tight tourniquet.

Necrosis and ulceration at site of bite due to direct venom effect or due to coagulopathy. Blistering in cobra bite is followed by superficial ulcer.

BLEEDING MANIFESTATION :

Oozing of blood from site of bite is first sign. Hemoptysis, Haematemesis, malena, Hematuria, Pyuria, Bleeding Gums are also seen. Early bleeding due to haemorrhagic activity.

RENAL SYSTEM :

Victims of viperbite have early proteinuria. Microscopic Hematuria occurs within first 24 to 48 hours.

Species responsible are Russel Viper and Echis Carinatus K.S.CHUGH et. al reported Acute Renal failure in 5 to 30% of cases of viper bite.

SHOCK

Shock remains most frequent cause of death in snake bite. Mortality is around 85 to 90% . Hypovolemia due to dehydration and hemorrhage can also cause shock. Over 50% of shock occurs within first 24 hours.

CARDIO VASCULAR SYSTEM

Tachycardia, Arrhythmias, ST-T Changes, Cardiac failure. Hyperkalemia due to hemolysis, Hemorrhages and renal impairment causes cardiac toxicity. Hydration and adequate urine out put to be maintained.

CENTRAL NERVOUS SYSTEM

In vipers CNS symptoms due to thrombosis or hemorrhage at different sites. Headache, confusion, blurring of vision, tingling, numbness, subarachnoid hemorrhage can occur. Venom does not cross blood brain barrier.

In elapid bites paralytic neuro symptoms develop from 30 minutes to 4 hours after bite. Ophthalmoplegia, Paralysis of tongue, throat and respiratory muscles occur. All these are reversible if treated early.

PITUITARY DYSFUNCTION

Panhypopituitarism due to pituitary hemorrhage occurs rarely.

MISCELLANEOUS

Anaphylactic reaction

Hypoglycemia

LABORATORY INVESTIGATIONS

1. COMPLETE HEMOGRAM

Hb% and Ht became low. Rised in Hypovolemia, Leukocytosis occurs in septic shock. Bleeding time is abnormal in only 50% of those with prolonged clotting time. Clotting time more than 15 minutes considered abnormal.

Prothrombin time and PTT are prolonged. Thrombocytopenia, Decreased fibrinogen, factor V, Factor VII occurs. Normal platelet count and unfragmented RBC's differentiates primary fibrinolysis from DIVC. Increased fibrin degradation products indicates fibrinolysis.

2. URINE ANALYSIS

Protein, Microscopic deposits, Specific Gravity, Osmolality, Myoglobin, HB should be done.

3. BIO - CHEMICAL

Urea, creatinine electrolytes, LFT, LDH, creatinine phosphokinase . Serum potassium and creatinine Kinase are elevated in Rhabdomyolysis. Serum cholesterol is inversely proportional to outcome. Decreased Cholesterol due to metabolism by phospholipase. A 2 in venom.

4. ECG

Atrio ventricular block, Changes of Hyperkalemia, ST – T Changes, QT prolongation.

5. Arterial blood gas analysis can be done to show metabolic acidosis, Hypoxia.

6. IMMUNO DIAGNOSTIC TEST

Like Elisa, to identify specific snake venom antigen in blood, urine and other body fluids.

MANAGEMENT

FIRST AID

Immobilize bitten limb using a splint. Application of tourniquet not too tight. Aim of tourniquet is to occlude lymphatic spread of venom. Good oral Hydration. Pain should be treated with paracetamol.

ANTI SNAKE VENOM (ASV)

Early administration of ASV to prevent complications .

INDICATIONS OF ASV :

Neurotoxicity

Hypotension

Shock

Coma

Bleeding abnormalities

Acute Renal Failure

DIVC

Rhabdomyolysis

ECG Changes

Evidence of intravascular hemolysis

Swelling more than Half of affected limb with extensive blistering and progress of local leision within 30 minutes.

CONTRA INDICATIONS

Atopic individuals , previous anti venom anaphylaxis

ASV is available in both monovalent and polyvalent forms. Monovalent ASV is useful if snake is definitely known and dosage required is half that of polyvalent antivenom. More than 100 types of antisnake venom produced by 26 laboratories .

Never too late to start ASV if systemic signs persist. Vipervenom can stay in circulation for 3 weeks. Hence, late ASV administration is also useful.

DOSAGE

To decide about dosage of ASV snake bite can be graded as follows :

Grade	Features	Dosage
Grade – I	Fang Marks + , Local Swelling Hemorrhage, Parasthesia	50 ml of ASV IV infusion
Grade – II	Fang Marks +, Local Swelling No systematic reaction	100 - 150 ml of ASV IV infusion in normal saline over 2 hours.
Grade - III	Swelling Progressing beyond site of bite, systemic reaction + laboratory changes. History of Bite by toxic	150 – 200ml of ASV as above

	snake.	
Grade – IV	Rapidly progressive swelling, echymosis, several generalized systemic signs and symptoms + Laboratory abnormalities History of multiple bites. Highly toxic snake	200 ml of ASV as above repeated doses depending on clotting time.

50 – 60 ml of ASV repeated every 4 to 6 hours till clotting time normalizes. Clotting time should be repeated every 4 – 6 hours for 48 hours ideally for 5 days and ASV repeated if necessary. ASV can be administered up to 3 weeks following snake bite as venom can remain active until then.

ADMINISTRATION

Freeze dried powder is reconstituted with 10ml of injected water. Test doses are administered on one forearm with 0.02ml of 1 : 10 solution intradermal. Appearance of erythema morethan 10mm within 30 minutes taken as positive test.

SIDE EFFECTS

Type - I

Immediate, Ig E mediated manifesting as restlessness, cough, itching, urticaria, tachycardia, Hypotension can occur. This is managed by 0.5 - 1.0ml of adrenalin given along with intramuscular antihistamines .

Type - II

Non – IgE mediated, characterized by hypotension, due to direct mast cell degranulation, anti histamines, volume expansion .

Type – III

Most common, due to delayed type - III IgM or IgG mediated serum sickness characterized by arthralgia, lymphadenopathy, malaise. This response is benign easily treated with steroids and anti histamines.

OTHER TREATMENTS

1. Local care and treatment to prevent loss of limb. Proper wound care and dressing to be done. Measurement of intracompartmental pressure and if more than 45mm indicates high risk of ischemic necrosis. In this cases fasciotomy done.
2. Heparin – if there is definite evidence of DIVC.
3. Steroid – benefit in capillary leak syndrome, also used in anaphylactic shock.
4. Blood – fresh blood, fresh frozen plasma, crypoprecipitate, platelets.
5. Neostigmine – in neuroparalytic elapid bites administered with atropine to mask muscuranic effects. If patients has respiratory paralysis assisted ventilation.
6. Dialysis – renal failure is managed either conservatively or with dialysis

INDICATIONS FOR DIALYSIS

CLINICAL - Anuria more than 48 hours

Detoriation of general condition

Hyperkalemia

Pulmonary edema

Severe acidosis

BIO CHEMICAL - Blood urea more than 120mg %

Serum creatinine more than 5mg%

Daily rise of urea more than 50% mg%

Daily rise of creatinine more than 1mg%

Daily fall of bicarbonate more than 2 meq per liter

Daily increase in potassium more than 1meq /l

In case of non oliguric renal failure the decision on dialysis depends on raising biochemical values.

Hemodialysis is preferred for those patients who are hemodynamically stable. In unstable patients with DIVC peritoneal dialysis is preferred. Usually acute renal failure patients recover within 3 weeks. If renal failure persist more than 3 weeks this is suggestive of cortical necrosis and biopsy is medial.

AIM OF STUDY

1. Clinical presentation of patients with snake bite induced renal failure.

2. Coagulation abnormalities.

3. Outcome in renal failure due to snake bite.

MATERIALS AND METHODS

Patients admitted in Government Mohan Kumaramangalam Medical College, with snake bite induced renal failure and coogulation abnormalities were examined from 10/2004 - 3/2006 - 50 Patients.

History was elicited about type of snake, site of bite, time of bite, the native treatment taken, symptoms like oliguria, bleeding tendencies and cellulitis.

CLINICAL EXAMINATION

LOCAL EXAMINATION

Site of snake bite is examined for presence of cellulitis , fang marks, bleeding from site of bite, local necrosis, gangrene.

GENERAL EXAMINATION

Vital signs like pulse, blood pressure, respiratory rate, sub conjunctival hemorrhage, echymosis, bleeding from bite site, periorbital edema, ptosis, extra ocular movement, cardiovascular system, respiratory system, abdomen, centralb nervous system examined.

INVESTIGATIONS

1. Coogulation profile – Clotting time, bleeding time, hemoglobin, total count, differential count, prothrombin time, Platelet count, fibrinogen, fibrin degradation products.
2. Liver function tests - serum bilirubin, SGOT, SGPT,. Alkaline phosphatase, total protein , albumin, globulin.
3. Renal Parameters – blood urea, serum creatinine, electrolytes Urine – Albumin, Sugar, RBC, WBC, Deposits.
4. Serum Cholesterol
5. Serum Uric Acid
6. Serum Calcium
7. Electrocardiogram

ROUTINE TREATMENT GIVEN

1. Injection TT 0.5ml. Subcutaneous on admission
2. If signs of envenomation present polyvalent ASV given.
3. Antibiotics -- Ampicillin, cefotaxime, metronidazole.
4. Parameters like clotting time, worsening of Renal failure watched. If no improvement occurs ASV repeated as 50ml each time until parameters are normalized.
5. Urinary output monitored and renal parameters watched regularly . Fluids and electrolytes maintained . Peritoneal dialysis and hemodialysis done depending on indications .
6. Blood transfusion and dopamine administered when patients are in shock.
7. Anti inflammatory drugs and wound care given accordingly.
8. ASV allergy treated with injection chlorpheniramine maleate and dexamethasone 8 m.g. and injection adrenaline. Dosage repeated if no significant improvement takes place ASV drip restarted and carefully watched for reaction.

COMPOSITION OF POLYVALENT ASV (1 ml)

0.6mg of dried Cobra Venom

0.45 mg of dried Krait Venom

0.6mg of Russels Viper dried Venom

0.45mg of dried Sawscaled Viper Venom

RESULTS

1. SEX DISTRIBUTION

SEX	NO.OF PTS	PERCENTAGE
Male	30	60
Female	20	40
Total	50	

M : F = 3 : 2

2. AGE DISTRIBUTION

SEX	NO.OF PTS	PERCENTAGE
11 - 20	8	16
21 - 30	10	20
31 - 40	14	28
41 - 50	11	22
51 - 60	5	10
61 - 70	2	4

From the above tables we can infer that incidence of snake bite is more among males and the age group commonly affected is between 31–40 years.

3. TYPES OF SNAKES

TYPES OF SNAKE	NO.OF PTS	PERCENTAGE
Viper	20	40
Un Identified	23	46
Cobra	7	14

4. TIME DELAY IN SEEKING MEDICAL ATTENTION AFTER SNAKE BITE

TIME DELAY OF OR BITE	NO.OF PTS	PERCENTAGE
< - 6 Hours	24	48
> - 24 Hours	14	28
1 – 2 day	7	14
2 – 4 day	4	8
4 - 5 day	1	2

We can infer from the above tables that viper bites accounts for nearly 40% of snake bites in our area more than 80 – 90% culminate in ARF.

5. SITE OF BITE

UL	6	12%
LL	43	86%
Other area (Lumbar)	1	2

6. SYMPTOMS

SYMPTOMS	NO OF PTS	PERCENTAGE
Pain & Swelling	50	100
Bleeding from site of Bite	15	30
Hematuria	35	70
Oliguria	32	64
Haematemesis	5	10
Anuria	2	4
Bleeding Gums	7	14

From above tables we can come to a conclusion that lower limb is the commonest site of bite. Pain is the commonest symptom encounted in almost all patients.

7. SIGNS

SIGNS	NO. OF PTS	PERCENTAGE
Cellulitis	50	100
Sub Conjunctival Hemorrhage	8	16
Hypotension	7	14
Gangrene and Local Necrosis	5	10
Hemiplegia	1	2
Seizures	2	4

From the above table we can infer that Cellulitis is seen in all patients.

8. RENAL PARAMETERS

BL.UREA	NO. OF PTS	PERCENTAGE
< 50	9	18
50 – 75	13	26
76 – 100	10	20
101 – 150	10	20
150 – 200	2	4
201 – 250 (Maximum)	6	12

From the above table almost 60% of patients had blood urea levels in the range 50 – 150mg%.

9. CREATININE

CREATININE mg/dl	NO. OF PTS	PERCENTAGE
1 - 2	10	20
2 - 3	12	24
3.1 - 5	10	20
5.1 - 7	7	14
7.1 - 9	5	10
9.1 - 11	4	8
11.1 – 15 (Maximum)	2	4

10. CT PROLONGATION IN PATIENTS

CT	NO. OF PTS	%
< 10	12	24
11 - 15	17	34
16 - 20	14	28
> 20	5	10
> 1 Hr	2	4

From the above tables in our study 60% patients had creatinine levels in the range of 2 – 7mg%.

11. PLATELET COUNT

	No. of PTS	%
1.5 – 3 L	18	36
1.0 – 1.5 L	26	52
50,000 – 1L	4	8
< 50,000	2	4

12. NO OF VIALS OF ASV

NO . OF VIALS	NO. OF PTS	%
< 5	6	12
6 – 10	5	10
11- 20	19	38
21 – 30	15	30
31 - 40	5	10

From the above study almost 70% of patients required mean ASV between 11 – 30 vials. 2 patients had platelet count < 50000 & highly prone for DIVC.

13. NO.OF DIALYSIS IN PATIENTS

NO. OF DIALYSIS	P.D	H.D	NO.OF PTS
0	-	-	13
1	30	8	22
2	2	5	2 + 5
3	-	2	2
4	-	2	2
8	-	8	1
13	-	13	2
22	-	22	1

22 Hemodialysis - In a case of patchy cortical necrosis proved by renal biopsy

14. DURATION OF HOSPITAL STAY

NO . OF DAYS	NO.OF PTS
< 5	10
6 - 10	6
11 - 15	21
16 - 20	10
21 - 30	2
> 31 days	1

Duration of Hospital Stay more than 31 days up to 3 months in a case of snake bite leading to patchy cortical necrosis.

15. SEASONAL VARIATION OF NO OF PATIENTS AND MORTALITY

MONTHS	NO.OF PTS.	NO.OF PTS. EXPIRED
July & Aug	4	Nil
Sep & Oct	6	2
Nov & Dec	4	1
Jan & Feb	11	2
March & April	18	Nil
June & July	3	Nil
Aug & Sep & Oct	3	Nil

From the above table we can infer that incidence of snake bite mortality was more in the months of March, April, September, October.

DISCUSSION

Snake bite envenomation is a major cause of death and disability in developing countries particularly in India on South East Asia. The percentage of hospitalization of all snake bite cases is only 10% of total snake bite.

Snake bite has seasonal variation the incidences more common during rainfall and summer. This is shown in a study of clinico epidemiological study in Nepal by Handsak and callor. In study of 50 cases of snake bites the number of cases and mortalilty both were more during March, April, September, and October.

The commonest snake causing renal failure was viper (CHUGH et al, 1989) In the study only in 27 cases snakes were identified. 20 of them were vipers.

In a study conducted by Chugh (1989) mean age of snake bite victim was 27years. In this study age group of patients were between 6 years to 70 years. Commonest age group was between 21 – 50 years. Mean Age was 43 years. Males were commonly affected. In a study by Chugh out of 70 cases 58 cases were males. In this study 30 cases were male patients.

Commonest site of bite was lower limb in 2/3 of patients in a study by Silveria. In our study in 43 patients site of bite was lower limb(86%). Fang mark present in 47% of cases by Silveria et al (1982). In our study fang mark present in 72% of patients. The mean time delay between bite and Medical help was 3 hours by Silveria et al. Increased time interval was associated with increased mortality .

In our study 35% reached the hospital before 6 hours, 38% reached between 6 – 24 hours, 7% between 24 – 48 hours, 14% after 48 hours. Mortality was less in patients admitted before 6 hours and after 4 days associated with increased mortality.

Chugh et al (1989) reported earliest symptom after snake bite is pain and swelling. Blister and local necrosis were present in 40% of cases. Haematemesis, Hematuria, Malena was present. In our study pain swelling and cellulitis was present in all cases. Local necrosis, gangrene was present in 5 cases. Sub conjunctival hemorrhage in 16% cases. Haematemesis in 10%.

In a study of 70% patients Chuge reported Oliguria in 66 patients. In our study 64% of patients had Oliguria. Hematuria was present in 70%. 2 patients had Anuria. 2 patients had seizures. 1 patients had Hemiplegia. Updhuya and Moorthi has reported the cases of ischemic cerebro vascular accident, ARF, DIVC following snake bite.

In our study 7 patients had ptosis out of them only 3 recovered 7 patients had hypotension at time of admission only 4 patients survived. Chugh reported hypotension in 11 out of 70 patients. Hypotension was attributed to bleeding, hypovolemia, depression of medullary vasomotor center. Myocardial depression, Arteriolar vasodilatation and increase vascular permeability.

In the study mortality in patients admitted with hypotension was 64%. Mean no of ASV and dialysis required in these patients were more compared to other patients.

Mean Blood urea level in study by Chugh 233 $\pm$ 10. Mean creatinine level was 9.2 $\pm$ 3.4. In our study mean urea was 146.4. Mean creatinine was 6.6. There was no correlation between peak urea level and severity. This difference may be due to earlier intervention by renal replacement therapy.

There are many studies showing DIC in snake bite. Acharya, Kanna had reported DIC in 24 out of 50 cases. Chugh reported 56% of patients having DIC. Desilva also reported DIC following snake bite. In our study 38% of patients had prolonged clotting time. Prothrombin time was prolonged 50% of patients. APTT was prolonged in 64% patients. Patients with prolonged APTT required more number of dialysis and ASV required was more compared to other patients.

Warell et al and Bhat reported presence of Mild to moderate proteinuria in snake bite victims. In this study all patients had albuminuria. 16% of patients had casts in urine. Non specific ECG changes including alternation in rhythm, bradycardia, tall T waves, non specific ST – T changes. In our study one patients had tall T waves.

Bhat observed that mean ASV dosage required was 120ml. Desilva reported mean ASV dosage has 190+95. In the study mean dosage of ASV was 190ml. The requirement of ASV was more in patients with hypotension, SCH has per Au Chan early administration of ASV had no benefit in preventing renal failure. In 50 patients 20 had received ASV before admission. Out of 5 patients expired 3 patients received ASV before admission among survived 2 patients required 500ml of ASV.

Chugh reported allergic reaction to ASV to be 15%. In this study only four patients developed allergy to ASV. All had itching and vomiting 1 patient had numbness of extremities. 1 patient had rash. All responded to injection pheniramine maleate and hydrocortisone.

Silveria in a study of 12 cases of ARF following snake bite reported 10 patients required dialysis. Sastri in a study of 19 patients reported good response to dialysis. Chugh reported in a study of 5 cases requirement of dialysis in 3 patients.

In our study 13 patients did not required dialysis. They were treated with fluid correction, antibiotics and conservative management. All other patients require peritoneal or hemodialysis. Mean dialysis required was 2. 1 patient required 22 hemodialysis. 13 patients required blood transfusion.

Duration of hospital stay was between 5 to 30 days among patients survived. 1 patient was hospitalized for nearly 3 months. According to Moorthy mortality was 10%. In our study mortality was also 10%. Patients presenting with bleeding tendency had increased mortality. Patients presenting with hypotension and coagulation abnormalities were also associated with increased mortality.

5 patients expired 3 cases received ASV before admission 2 cases received ASV after admission. One died 1 day after, 2 died 5 days after admission 1 died 6 days after admission, 1 died 11 days after admission.

CONCLUSION

1. Seasonal variation was present in snake bite. Incidence and mortality more during January, February, March, April.

2. Males were commonly affected, lower limb being commonest site of snake bite.

3. Of the identified snakes viper bite was the commonest cause of acute renal failure following snake bite.

4. ARF due to snake bite may be both Oliguric and Non – Oliguric of which Oliguric accounts for 90% and Non – Oliguric accounts for 10%.

5. Renal lesion due to snake bite may be of two types – of which Acute tubular necrosis accounts for 70 to 80%, acute cortical necrosis accounts for 20 to 30%.

6. Oliguria which lasts for 4 to 15 days suggests the possibility of acute cortical necrosis which carries worst prognosis.

7. Hypotension, Sub conjunctival hemorrhage, disorientation, Seizures, Hemiplegia, anuria, during presentation were associated with increased mortality.

8. Mortality was less in patients who came with in 6 hours. Mortality was more in patients who came after 6 hours - 4 days of snake bite

9. Majority of patients had hypoalbuminemia and this was correlated with increased morbidity and mortality.

10. Mortality rate was 10%. Early adequate dosage of ASV was associated with better prognosis. Early detection of renal failure and institution of dialysis was associated with better outcome.

11. Commonest cause of mortality was coagulation abnormalities.

SUMMARY

Snake bite is an occupational hazard in this part of country. It account for nearly 10% of Hospital admissions in this place and associated with increased mortality.

For this purpose the study has been carried in this place. From this study we have come to inference that early treatment with anti snake venom, adequate hydration and prevention of hypotension causes reduce mortality due to ARF from snake bite envenomation.

Early adequate dosage of ASV was associated with better prognosis. Early detection of renal failure and institution of dialysis was associated with better outcome.

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