"STUDY OF ACUTE KIDNEY INJURY IN SNAKE BITE PATIENTS"

By

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Dissertation submitted to BLDE (Deemed to be University), Vijayapura
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DOCTOR OF MEDICINE

IN

GENERAL MEDICINE

Under the guidance of

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LIST OF ABBREVATIONS

ADQI	👁	Acute Dialysis Quality Initiative
AKI	👁	Acute Kidney Injury
AKIN	👁	Acute Kidney Injury Network
ASV	👁	Anti Snake Venom
DIC	👁	Disseminated Intravascular Coagulation
MDRD	👁	Modification of Diet in Renal Disease
WBCT	👁	Whole Blood Clotting Time

ABSTRACT

BACKGROUND AND OBJECTIVE

Snake bite poisoning is known to man since antiquity. The complications related to kidneys are observed in majority of patients with poisonous snake bite.

This study is an attempt to study the clinical profile of snake bite patients and evaluation of acute kidney injury in them.

METHODOLOGY

Sixty five patients with history of snake bite who satisfied inclusion and exclusion criteria were selected randomly and their clinical profiles were assessed. AKI was evaluated using noninvasive methods.

RESULT

Out of 65 patients in the study, majority were males (62%) with mean age of presentation 43.8±12.63 years. The mean interval between snakebite and presentation to Hospital was 10 hours.20 patients (31%) of patients had AKI.

86% patients presented with local signs of inflammation, 49% of patients presented with coagulation abnormality and 28 patients (43%) were having decreased urine output ,of which 75% (15 patients) were associated with AKI.

INTERPRETATION AND CONCLUSION

Common manifestations of poisonous snake bite include cellulitis, abnormal coagulation profile & decreased urine output. Overall mortality due to snake bite induced AKI is 4.6%. Lapse of time in presenting to the hospital and abnormal coagulation profile are the predictors of poor outcome.

KEY WORDS: Snake bite; AKI; Snakebite induced AKI; Coagulation profile; Lapse of time; Decreased urine output

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INTRODUCTION

SNAKE BITE POISONING is known to man since antiquity. Bite rates are highest in temperate and tropical regions where populations subsist by manual agriculture. In India, a large proportion of snake bites occur when people are working barefoot in the fields or while walking at night. Recent estimates indicate somewhere between 1.2 million and 5.5 million snakebites worldwide each year, with 421,000-1,841,000 envenomations and 20,000– 94,000 deaths.[4] Several educational and preventive actions should be taken in order to protect farm workers, who are the main victims of such accidents.[8]

The complications related to kidneys are observed in majority of patients with poisonous snake bite. Such renal failure, usually due to acute tubular necrosis, is frequently reversible. If bilateral cortical necrosis occurs, however the prognosis of renal recovery is more grim.[4]

The study is an attempt to study the clinical profile of snake bite patients and evaluation of acute kidney injury in them.

OBJECTIVES

1. To study the clinical profile of renal involvement in snake bite patients
2. To study the in-hospital outcome of acute kidney injury in snake bite patients

REVIEW OF LITERATURE

HISTORICAL REVIEW

Snakes were both revered and worshipped and feared by early civilizations. Historically, snakebites were seen as a means of execution in some cultures. The ancient Egyptians recorded prescribed treatments for snakebites as early as the thirteenth dynasty in the Brooklyn Papyrus, which includes at least seven venomous species common to the region today, such as the horned vipers.[1]

Sir William Osler in 1912 described several recognizable causes of AKI under the heading of 'acute Bright's disease' including sepsis, pregnancy, burns and toxins.[2]

In 1960, Steinbeck described a patient who developed nephritic syndrome following snakebite. In 1974, Seedat et al. reported two patients who developed glomerulonephritis following puff adder bite.[36]

SNAKE BITE

Most snakebites are innocuous and are delivered by nonpoisonous species. Worldwide, only about 15% of the more than 3000 species of snakes are considered dangerous to humans.[3]

Snakes are poikilotherms, which account for their distribution and activity, and mostly active around 25-35°C. 97% of snakebites are on the extremities. Males are bitten more frequently than females. 85% snakebites are predominate hemotoxin.

Venomous snakes belong to the families:
Viperidae (subfamily Viperinae: Old World vipers; subfamily Crotalinae: New World and Asian pit vipers)
Elapidae (including cobras, kraits, coral snakes and all Australian venomous snakes), **Hydrophiidae** (sea snakes), **Atractaspididae** (burrowing asps), and **Colubridae** (a large family

in which most species are nonvenomous and only a few are dangerously toxic to humans).[4]

Viperidae have relatively long fangs (solenoglyph) which are normally folded flat against the upper jaw but, when the snake strikes, they are erected. There are two subfamilies, typical vipers (Viperinae) and pit vipers (Crotalinae). The Crotalinae have a special sense organ, the loreal pit organ, situated between the nostril and the eye to detect their warm-blooded prey.[5] Viperidae are relatively short, thick-bodied snakes with many small rough scales on the top (dorsum) of the head and characteristic patterns of coloured markings on the dorsal surface of the body.[5]

Elapidae: have relatively short fixed front (proteroglyph) fangs. This family includes cobras, king cobra, kraits, coral snakes, Australasian snakes and sea snakes. Elapidae are relatively long, thin, uniformly-coloured snakes with large smooth symmetrical scales (plates) on the top (dorsum) of the head. There is no loreal scale between the preocular and nasal scales. Some, notably cobras, raise the front part of their body off the ground and spread and flatten the neck to form a hood. Many species of cobra can spit venom for more than one metre towards the eyes of their enemies.[5]

Other medically important venomous snakes

Two species of medically important Colubridae have been identified in the sea region, the red-necked keelback Rhabdophis subminiatus and Yamakagashi R.tigrinus.

Large pythons (Boidae), notably the reticulated python, Python reticularis in Indonesia, have been reported to attack and even ingest humans.[5]

The venom apparatus of poisonous snakes consists primarily of two components: a modified tooth, the fang by which venom is delivered into prey, and the venom gland (or glands) situated behind and below the eye where toxin is produced and stored. Venomous snakes use the

venom apparatus to rapidly kill prey and secondarily in defense from their own enemies.[6]

Larger snakes of the same species tend to have more venom, although the larger snake may have learned to ration its venom while a smaller and younger animal may be more likely to inject the full load. Moreover, the venom is stronger when the snake awakens from hibernation.[7]

Unfortunately, there is no simple rule for identifying a dangerous venomous snake. Some harmless snakes have evolved to look almost identical to venomous ones.

However, some of the most notorious venomous snakes can be recognized by their size, shape, colour, and pattern of markings, behaviour and the sound they make when they feel threatened. For example, the defensive behaviour of the cobras is well known, they rear up, spread a hood, hiss and make repeated strikes towards the aggressor. Colouring can vary a lot. However, some patterns, like the large white, dark-rimmed annular (ring) spots of the Russell's vipers or the alternating black and yellow circumferential bands of the banded krait are distinctive. The blowing hiss of the Russell's viper and the grating rasp of the saw- scaled viper are warning and identifying sounds.[5]

VENOM COMPOSITION: More than 90% of snake venom is protein. Each venom contains more than a hundred different proteins: enzymes (constituting 80-90% of viperid and 25-70% of elapid venoms), non-enzymatic polypeptide toxins, and non-toxic proteins such as nerve growth factor.[5]

Venom enzymes[5]

These include digestive hydrolases, hyaluronidase, and activators or inactivators of physiological processes, such as kininogenase. Most venoms contain , phosphomono- and diesterases,1-amino acid oxidase, 5[1]-nucleotidase,NAD-nucleosidase,DNAase, peptidases and phospholipase A2.

Zinc metalloproteinase haemorrhagins : Damage vascular endothelium, causing bleeding.

Procoagulant enzymes: Venoms of Viperidae, some Elapidae and Colubridae has serine proteases and other procoagulant enzymes that are thrombin like and activate factor X, prothrombin and other coagulating factors.

Phospholipase A2 (lecithinase): The most widespread and extensively studied of all venom enzymes. It damages important structures of the cell like mitochondria, RBC, WBC and platelets, peripheral nerve endings, skeletal muscle, endothelium lined membranes, produces presynaptic neurotoxic activity, sedative effects like opium, leads to the autopharmacological release of histamine and anti- coagulation.

Hyaluronidase: Promotes the spread of venom through tissues. Proteolytic enzymes like metalloproteinases, endopeptidases and hydrolases and polypetide cytotoxins like cardiotoxins leads to increase in vascular permeability that leads to oedema, blistering, bruising and necrosis at the site of snakebite.

Venom polypeptide toxin (neurotoxins)

Venoms often contain different neurotoxins that work synergistically to cripple the nervous system. Neurotoxins can be classified according to their site of action: pre-synaptic neurotoxins block neurotransmission by affecting acetylcholine transmitter release; post-synaptic neurotoxins are antagonists of the acetylcholine receptor.[13] Postsynaptic (α) neurotoxins such as α-bungarotoxin and cobrotoxin bind to acetylcholine receptors at the motor endplate. Presynaptic (β) neurotoxins such as "β-bungarotoxin, taipoxin and crotoxin" contain 120-140 amino acids and a "phospholipase A subunit" block acetylcholine transmitter release.

In ≈20% of pit viper bites and higher percentages of other snakebites (up to 75% for sea snakes), no venom is released ("DRY" BITES). Significant envenomation probably occurs in ≈50% of all venomous snakebites.[4]

SYMPTOMS AND SIGNS OF SNAKE BITE

Snake venoms are extremely complex substances. They have proteic and non-proteic fractions, and may produce local changes, such as acute inflammatory activity, edema, ecchymosis, blisters and necrosis, and systemic changes, such as hemorrhage, blood pressure alteration, neurotoxicity, hemolysis, rhabdomyolysis and acute kidney injury (AKI). Renal injury is the leading cause of death among patients surviving the early effects of venom, and the most frequent renal histological injury found in venom-induced AKI is acute tubular necrosis.[8] Acute renal failure in Russell viper bites is due to toxic nephropathy and prolonged hypotension due to delay in seeking treatment.[9]

Early symptoms and signs[5]

Following the immediate pain of mechanical penetration of the skin by the snake's fangs, there may be increased local pain. However, bites by kraits, sea snakes and Philippine cobras may be virtually painless and may cause negligible local swelling. Someone who is sleeping may not even wake up when bitten by a krait and there may be no detectable fang marks or signs of local envenoming.

Local symptoms and signs in the bitten part[5]

- 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

Soft tissue infection is a major complication of snakebite with local envenoming. The proteolytic properties of snake venom cause extensive tissue destruction and devitalization, thus predisposing the wound to bacterial infection from the snake's indigenous oral flora. Atul et al. found that gram positive bacteria are more common than gram negative and the most common gram positive bacteria in venom is Staphylococcus aureus followed by coagulase negative Staphylococcus and Streptococcus species.[10]

Generalized (systemic) symptoms and signs[5]

General : Nausea, vomiting, malaise, abdominal pain, weakness, drowsiness and prostration.

Cardiovascular: Dizziness, faintness, collapse, shock, hypotension, cardiac arrhythmias, pulmonary oedema.

Bleeding and clotting disorders Traumatic bleeding from recent wounds, spontaneous systemic bleeding – from gums, epistaxis, bleeding into the tears, intracranial hemorrhage haemoptysis, haematemesis, bleeding into the mucosae, skin and retina.

Neurological : Drowsiness, paraesthesia abnormalities of taste and smell, "heavy" eyelids, ptosis, external ophthalmoplegia, difficulty in swallowing secretions, respiratory and generalised flaccid paralysis.

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

Renal Loin pain, hematuria, haemoglobinuria, myoglobinuria, acute kidney injury.[5]

Long-term complications (sequelae) of snake-bite

At the site of the bite, loss of tissue may result from sloughing or surgical debridement of necrotic areas or amputation. Chronic ulceration, infection, osteomyelitis, contractures, arthrodesis or arthritis may persist causing severe physical disability. Malignant transformation may occur in skin ulcers after a number of years.[7]

Chronic kidney disease (renal failure) occurs after bilateral cortical necrosis and chronic panhypopituitarism or diabetes insipidus after Russell's viper bites are reported from Myanmar and South India. Chronic neurological deficit is seen in the few patients who survive intracranial haemorrhages and thrombosis (Viperidae).[5] There are reports of Guillain-Barre syndrome, and delayed neuropathy, following snake bite.[11]

Symptoms and signs of cobra-spit ophthalmia (eye injuries from spitting cobras)[5]

If the "spat" venom enters the eyes, there is immediate and persistent intense burning, stinging pain, followed by profuse watering of the eyes with production of whitish discharge, congested conjunctivae, spasm and swelling of the eyelids, photophobia, clouding of vision and temporary blindness. Corneal ulceration, permanent corneal scarring and secondary endophthalmitis are recognised complications.

SNAKEBITE PREVENTION AND TREATMENT PROTOCOL

Lack of concentration, overconfidence, and a lack of protective measures, such as wearing gloves, boots, or long pants, in activities and work in places where snakes are hidden are some of the causes of snakebites.[7] Of primary importance is the need to recommend the most effective first aid for victims, to enable them to reach the nearest health care centre facility in the relatively stable condition. Most of the first aid practises carried out are ineffective and dangerous.[12]

Delay in seeking medical aid or ignorance among primary care physicians about the correct treatment of snake-bite is responsible for the high morbidity and mortality.[9]

Appropriate first aid is of vital importance for snake-bite victims. Many measures which were advocated earlier have now been abandoned as being harmful. These include the tying of tight (arterial) tourniquets, incising and bleeding the wound, sucking the wound to remove the venom from it and the local application of ice.[9]

Recommended first-aid measures include the use of a wide, flat constriction band applied proximal to the bite to block only superficial venous and lymphatic flow. This should be left in place until antivenom therapy, if indicated, is begun. The band should be loose enough to permit one or two fingers to slide easily beneath it. Excess constriction could impair arterial blood flow and lead to tissue death. Excess activity, such as walking, should be avoided. The bitten extremity should be immobilized and kept in a dependent position. The victim should be rapidly transported to the nearest hospital.[9]

DIAGNOSIS PHASE[12]

Inquire about the time the bite occurred and details about the onset of pain.

Early and intense pain implies significant envenomation.

20 Minute Whole Blood Clotting Test (20WBCT)

It is the most accurate test of coagulation that can be done at bedside. 3 to 5 ml of venous blood ample of fresh venous blood is taken in a glass test tube and left at room temperature for 20 minutes. It is important that the tube is clean glass and dry as the mechanism under review is the contact clotting mechanism. The use of plastic bottles, tubes or syringes will give false readings and should not be used. The glass vessel should be left undisturbed for Twenty minutes and then gently tilted,without shaking. If the blood is still liquid then the patient has incoagulable blood. The vessel

must not have been washed with detergent as this will inhibit the contact element of the clotting mechanism. Test should be carried out every 30 minutes from admission for three hours and then hourly after that. If incoagulable blood is discovered, the 6 hourly cycles will then be adopted to test for the requirement for repeat doses of ASV.

Other Tests based on availability are

- Haemoglobin/,Packedcellvolume,/PlateletCount/ProthrombintimeT/ActivatedPartialTromboplastin time,Fibrin degradation products,D-Dimer ,
- Peripheral Smear
- Urine Tests like Proteinuria, Red blood cell, Haemoglobinuria, Myoglobinuria
- Biochemistry for Serum Creatinine, Urea, Potassium,
- Oxygen Saturation, Pulse rate, Blood Pressure, Respiratory Rate, Postural Blood Pressure,
- EKG, Radiograph, CT, Sonogram.

The use of Radiograph and USG are not useful, apart from identification of bleeding in Viper snake bites.

A neutralizing antibody gives antivenin efficacy. Two kinds of antivenin are available. One has been manufactured since 1956. It is derived from horse serum after the horse is injected with sublethal doses of snake venom (Wyeth). The antivenin is purified but still contains other serum proteins that can be immunogenic. The latest version, approved by the US Food and Drug Administration (FDA) in 2000 (CroFab, Savage), is a monovalent immunoglobulin fragment derived from sheep but purified to avoid other antigenic proteins.[3]

ASV administration criteria[12]

As per the W.H.O. SEARO Guidelines ONLY if a patient develops one or more of the

following signs/ symptoms should ASV be administered.

Systemic envenoming

- Evidence of coagulopathy: detected by Twenty minute Whole Blood Clotting Time and signs like spontaneous bleeding from gums etc.
- Signs of neurotoxicity: ptosis, external opthalmoplegia, inability to lift the head etc
- Cardiovascular changes:fall in BP, shock, arrhythmias, abnormal Electrocardiogram
- Acute renal failure
- Hemoglobinuria/ myoglobinuria: dark brown urine
- vomiting and abdominal pain

Local envenoming[12]

- swelling affecting more than half of the snake bitten limb (in the absence of a tourniquet). In the case of severe swelling after bites on the digits (toes and especially fingers after the bite of a known necrotic species).
- Rapid extension of swelling
- Development of enlarged tender lymphnodes draining the bitten limb.

The recommended dosage level has been based on published research that Russells Viper injects on average 63 mg SD 7 mg of venom (Tun Pe, 1986). Therefore initial dose should be calculated to neutralise the average dose of venom injected. This ensures that the majority of victims should be covered by the initial dose. The range of venom injected is 5 mg – 147 mg. This suggests that the total required dose will be between 10 vials to 25 vials as each vial neutralises 6 mg of Russells Viper venom.

Test doses have no predictive value in detecting anaphylactoid and late serum reactions and

should not be used[12]

Anti Snake Venom can be administered in two ways:

1.Intravenous bolus dose reconstituted or liquid ASV is administered by slow intravenous injection at the rate of 2 ml/minute.

2.Continuous infusion of liquid or reconstituted Anti snake venom is diluted in Normal saline or glucose should be given at the rate of 5-10 ml/kg body weight .

All ASV is to be administered over 1 hour.

ASV REACTION[12]

Anaphylaxis is life-threatening, but despite the reluctance in giving ASV due to reactions (Kalantri et al., 2005), if the protocol is followed, it can be effectively treated and dealt with. Anaphylaxis can be of rapid onset, and can deteriorate to life threatening emergency very quickly.

ASV should be discontinued

Start the patient on oxygen,start fresh iv normal saline infusion with a new iv set .Administer adrenaline (1 in 1000 solution) 0.5mg (0.5ml)in adults IM. In Children it is given 0.01 mg/kg body weight of adrenaline IM. In addition, to provide longe term protection against anaphylactoid reaction, 100 mg of hydrocortisone and 10 mg of chlorpheniramine maleate (H_1 antihistamine) for adults and 0.2 mg/kg in children should be administered IV.

The dose for children is 0.2 mg/kg of antihistamine IV and 2 mg/kg of hydrocortisone. After the patient has recovered, the ASV can be restarted slowly by keeping the patient under close observstion.

Pregnant women are treated the same way as other victims and the same dosage of ASV is given.

Neurotoxic Envenomation[12]

Neostigmine is an acetylcholinesterase inhibitor which leads to increase in Ach by preventing its degradation therefore reverse respiratory failure and neurotoxic symptoms. It is particularly effective for post synaptic neurotoxins such as those of Cobra. But in case of presynaptic neurotoxic venom of krait and southern russells viper its usefulness is not proven.

In the case of neurotoxic envenomation, the 'Neostigmine Test' should be performed by administrating: 1.5-2.0 mg of neostigmine IM, together with 0.6 mg of atropine IV. The paediatric neostigmine dose is 0.04 mg/kg IM and the dose of atropine is 0.05 mg. Patient should be observed closely for 1 hour to know the response to neostigmine.

Clinically it can be assessed by the following:

1. Number of millimetres of iris uncovered
2. Inter incisor distance
3. Length of time upward gaze can be maintained
4. Single breath count

In case of neurotoxic snake bite atropine 0.6 mg followed by neostigmine 1.5 mg to be given i.v stat and repeat dose of neostigmine 0.5 mg with atropinr every 30 mins for five doses.there after to be given as tapering dose at 1 hr,2 hr,6 hr and 12hr .Majority of the patients improve with in first 5 doses, repeat Doses: antisnake venom[12]

In the case of vasculotoxic snake bite, inial dose of ASV should be given over one hour if their is coagulation abnormality . And coagulation profile should be repeated after six hours if abnormality still persists second dose of ASV should be given if it is normalizes then ASV can be stopped.

Hypotension[12]

Hypotension can be due to many causes, mainly it is due to haemorhage leading to decreased blood volume, vasodilation due to the action of the venom on the blood vessels or direct action of venom on the heart. Hypovolaemia is tested by measuring the blood pressure in the lying down position, as well as in the reclining state, to establish a postural drop.

Treatment is by means of plasma expanders and there is no conclusive evidence to support a preference for colloids or crystalloids. In cases where generalised capillary permeability has been established, a vasoconstrictor such as dopamine can be used.

Antibiotics are often given upon arrival to hospital but most likely benefit only severe cases. However, broad-spectrum antibiotic prophylaxis is still recommended.

Role of Heparin and Botropase in Viper Bites[12]

Heparin by reducing fibrin deposits helps in the treatment of disseminated intravascular coagulation.But in Viper bite patients thrombin formed due to Venom is resistant to heparin and can leads to bleeding.Hence it is contraindicated in viper bite patients .Moreover the effect of heparin on Antithrombin III negated because it is eliminated by the time heparin is administered.

Coagulants like botropase which is prepared from the venom of South American Pitvipers should be avoided because it causes consumption coagulopathy which prolongs coagulation abnormality in Indian viper bite patients.

ACUTE KIDNEY INJURY

Acute kidney injury (previously known as acute renal failure) is characterized by the

sudden impairment of renal function leading to retention of nitrogenous and other waste products normally cleared by the kidneys. AKI is a heterogeneous group of conditions that share common diagnostic features: specifically, an increase in the blood urea nitrogen concentration and/ or an increase in the blood or serum creatinine concentration often associated with decreased urine output .[4]

Acute kidney injury (AKI) is a common and serious complication in critically ill patients. The mortality rate remains high despite improved renal replacement techniques. Acute kidney injury is no longer considered to be an innocent bystander merely reflecting co-existent pathologies. It has been demonstrated to be an independent risk factor for mortality. The cause of this is unclear but is possibly associated with an increased risk of "non-renal" complications such as bleeding and sepsis [13].

It is recognized that the epidemiology of AKI in developing countries differs from that of the developed world in many important ways. Whereas in developed regions elderly patients predominate, in developing countries, AKI is a disease of the young and children, in whom volume-responsive "prerenal" mechanisms are common.[14]

AKI is a worsening problem, but its true incidence is unknown. From a worldwide perspective, there is a clear need to understand the epidemiology of AKI more accurately. Use of standardized definitions and descriptions of existing at-risk and high-risk populations, both in community and institutional settings in developing and underdeveloped countries, are the first steps to improve outcomes.[14]

Two prospective observational studies of 2576 people found that established acute renal failure affected nearly 5% of people in hospital, and as many as 15% of critically ill people,

depending on the definitions used.[15]

RISK FACTORS[15]

General risk factors: Risk factors for acute renal failure include: age,hypovolaemia, hypotension, sepsis, pre-existing renal, hepatic, or cardiac dysfunction, diabetes mellitus and exposure to nephrotoxins (e.g., aminoglycosides, amphotericin, immunosuppressive agents, NSAIDs, ACE inhibitors and intravenous contrast media).

Risk factors or aetiology in critically ill people: Isolated episodes of acute renal failure are rarely seen in critically ill people, but are usually part of multiple organ dysfunction syndromes. Acute renal failure requiring dialysis is rarely seen in isolation (<5% people). The kidneys are usually the first organs to fail.

CAUSES OF ACUTE KIDNEY INJURY[16]

- **Prerenal**:
  - Volume depletion (e.g. hemorrhage, severe vomiting or diarrhoea, burns, inappropriate diuresis)
  - Oedematous states: cardiac failure, cirrhosis, nephrotic syndrome
    - Hypotension (e.g. cardiogenic shock, sepsis, anaphylaxis)
    - Renal hypoperfusion non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists, abdominal aortic aneurysm, renal artery stenosis or occlusion, hepatorenal syndrome

- **Intrinsic acute kidney injury (AKI):**
  - Glomerular disease: glomerulonephritis, thrombosis, haemolytic uremic syndrome

- Tubular injury: acute tubular necrosis (ATN) following prolonged ischaemia; nephrotoxins (e.g. aminoglycosides, radiocontrast media, myoglobin, cisplatin, heavy metals, light chains in myeloma kidney)

- Acute interstitial nephritis due to drugs (e.g. NSAIDs), infection or autoimmune diseases

- Vascular disease: vasculitis (usually associated with antineutrophil cytoplasmic antibody), cryoglobulinaemia, polyarteritis nodosa, thrombotic microangiopathy, cholesterol emboli, renal artery stenosis, renal vein thrombosis, malignant hypertension

- Eclampsia

- **Postrenal:**
  - Calculus
  - Blood clot
  -
  - Papillary necrosis
  - Urethral stricture
  - Prostatic hypertrophy or malignancy
  - Bladder tumour
  - Radiation fibrosis
  - Pelvic malignancy
  - Retroperitoneal fibrosis

Symptoms[16]

Urine output:

- AKI is usually accompanied by oliguria or anuria, but polyuria may occur.

- Abrupt anuria suggests an acute obstruction, acute and severe glomerulonephritis, or acute renal artery occlusion.
- Gradual diminution of urine output may indicate a urethral stricture or bladder outlet obstruction, e.g. benign prostatic hyperplasia.

Nausea, vomiting

Dehydration Confusion

Signs[16]

- Hypertension
- Abdomen: may reveal a large, painless bladder typical of chronic urinary retention
- Dehydration with postural hypotension and no oedema
- Fluid overload with raised JVP, pulmonary oedema and peripheral oedema
- Pallor, rash, bruising: petechiae, purpura, and nosebleeds may suggest inflammatory or vascular disease, emboli or disseminated intravascular coagulation
- Pericardial rub

ADQI (Acute Dialysis Quality Initiative) workgroup identified a definition/ classification system for AKI. The workgroup considered that the definition of AKI necessarily required the following features: ease of use and clinical applicability across different centres; sensitivity and specificity for different populations and research questions; consideration of creatinine change from baseline; and implementation of classifications for acute on chronic renal disease.

Therefore a classification system is required which is able to distinguish between mild or moderate and early or late cases. Thus such a classification helps to detect patients with mild renal failure i.e with high sensitivity and low specificity and severe AKI i.e with high specificity and low sensitivity. According to this, a multilevel classification system was suggested, in which the

complete spectrum of acute renal dysfunction could be included, such as Risk of renal dysfunction, Failure or Loss of kidney function, Injury to the kidney and End-stage kidney disease; these criteria are identified by the acronym RIFLE. And if patients are admitted with AKI without any baseline measure of renal function, a theoretical baseline value of serum creatinine for a given patient assuming a normal glomerular filtration rate (GFR) should be estimated. By normalizing the GFR to the body surface area, and assuming a GFR of approximately 75–100 ml min^{-1} per $1.73m^2$, the 'modification of diet in renal disease' formula was selected by serum creatinine based on age,sex and race estimated GFR (ml min^{-1} per $1.73m^2$) = 186 $(SCr)^{-1.154}$ x $(age)^{-0.0203}$ Multiplied by 0.742 if female and 1.210 if black.[18]

The ADQI group first proposed the RIFLE system at the second ADQI Conference in Vicenza, Italy in May 2002 to define acute kidney injury. This classification system uses individual criteria for SCr levels and urine output (UO). Patients are classified into three severity categories (risk, injury, and failure) and two clinical outcome categories (loss and end-stage renal disease).[17] Being a definition, RIFLE is intended to establish the presence or absence of the clinical syndrome of AKI in a given patient or situation, and to describe the severity of this syndrome. The classification was not designed to predict mortality or adverse outcomes, although it is logical to assume that more severe disease should result in worse outcome.[18]

The RIFLE classification is not without its limitations.

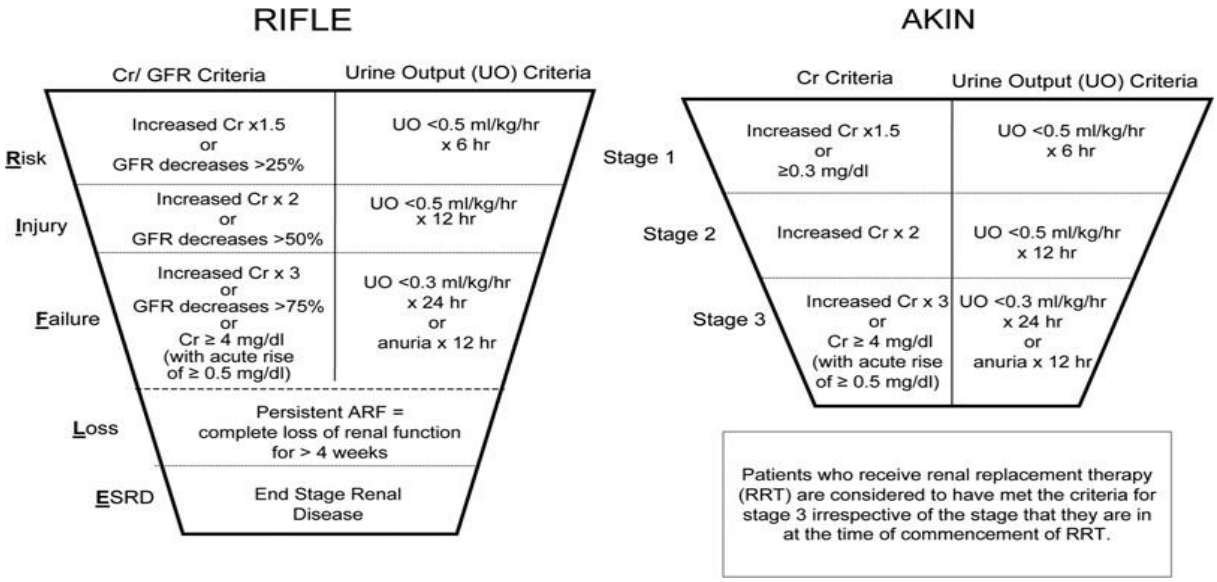
1. any clinical definition of AKI signals its presence when there has already been a decline in the GFR, whereas biomarkers are able to make the diagnosis at an earlier stage;
2. The use of 6-hour and 12-hour urine criteria make RIFLE unyieldy for retrospective studies,

since such data are not collected as part of routine clinical practice.

3. Limitation of RIFLE is that the creatinine/GFR criterion is based on change from a baseline value, which is often not available In this scenario, the ADQI recommends a creatinine estimation based on the Modification of Diet in Renal Disease (MDRD) formula, assuming a normal GFR of approximately 75 to 100 ml/min/1.73 m^2.
4. Recent studies have shown that smaller changes in creatinine than those specified under class Risk, such as an absolute increase as small as 0.3 mg/dl, are associated with poor outcomes.[18]

Because of the limitations of RIFLE, AKIN (Acute Kidney Injury Network) defined AKI as an abrupt (within 48 hours) increase in the serum creatinine of "≥ 0.3 mg/dl" (i.e 26.4 micromol/L) from initial value, a percentage increase in the serum creatinine of more than fifty percent, or urine output less than 0.5 ml/kg per hour for more than six hours.[19]

The AKIN classification differs from the RIFLE classification as follows: it reduces the need for baseline creatinine but does require at least two creatinine values within 48 h; AKIN stage 1 is similar to RIFLE-R but includes abrupt
(within 48 h) reduction in kidney function (increase in SCr ≥0.3 mg/dL); injury and failure are the same as stages 2 and 3, respectively; stage 3 also includes patients who need renal replacement therapy in any stage; two outcome classes, loss and end-stage kidney disease, are omitted.[17]



The distinction between pre-renal AKI and AKI due to parenchymal injury is potentially important because it is argued that correction of 'pre-renal factors' causing renal under perfusion may reverse pre-renal AKI, whereas neglecting these causes AKI to become irreversible. Reversal of AKI in less than 24–72 h after fluid replacement is the most common definition of pre-renal AKI.[20]

A low fractional excretion of sodium (FENa) and/or urea (FEurea) are often used to define pre-renal AKI, although diuretics and sepsis make interpretation of the FENa difficult and aging and sepsis alter FEurea.[20]

BIOMARKERS OF ACUTE KIDNEY INJURY

Accessible markers of AKI can be components of serum or urine or can be imaging studies or any other quantifiable parameter. The urine has yielded the most promising markers for the early detection of AKI and further characterization is anticipated, which will qualify these markers as useful tools for the earlier diagnosis, identification of mechanism of injury, and assessment of site and severity of injury.[21]

Serum creatinine, although used routinely in clinical practice and in clinical trials, is a poor

marker of renal dysfunction. Unlike serum troponin in myocardial infarction, an increase in serum creatinine is not directly related to tubular injury in AKI but is the effect of loss of filtration function that occurs with AKI. There is also a delay in the detectable increase in serum creatinine as a result of the time required for its accumulation and equilibration. Changes in creatinine can be nonspecific as they may occur as a result of several nonrenal factors, such as muscle mass and nutrition.[22]

Some of the urinary biomarkers of acute kidney injury are cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-glucosaminidase (NAG), c-glutamyl transpeptidase, IL-18, and kidney injury molecule-1 (KIM-1).

N-acetyl-β-glucosaminidase (NAG)

A proximal tubule lysosomal enzyme, has been extensively studied and has proven to be a sensitive, persistent, and robust indicator of tubular injury. Increased NAG levels have been reported with nephrotoxicant exposure, delayed renal allograft function, chronic glomerular disease, diabetic nephropathy, as well as following cardiopulmonary bypass procedures.[12]

β2-microglobulin (β2M)

β2M is an 11.8-kDa protein that is the light chain of the major histocompatibility class (MHC) I molecule expressed on the cell surface of all nucleated cells. β2M is typically filtered by the glomerulus and almost entirely reabsorbed and catabolized by the proximal tubular cells, a process that may be impeded in AKI.[21]

α1-microglobulin (α1M)

α1M is a 27−33-kDa protein synthesized by the liver with approximately half of the circulating protein complexed to IgA. The free form is readily filtered by the glomerulus and reabsorbed by proximal tubule cells. Unlike β2M, urinary α1M is stable over the range of pH

found in routine clinical practice, making it a preferred marker of tubular proteinuria in human bioassays.[21]

Retinol binding protein (RBP)

Is a 21-kDa protein that is hepatically synthesized and responsible for transporting vitamin A from the liver to other tissues. It is freely filtered by the glomerulus and subsequently reabsorbed and catabolized by the proximal tubule. Bernard et al. monitored patients with AKI from various etiologies and found urinary RBP to be a highly sensitive indicator of renal tubule dysfunction, preceding urinary NAG elevation. They reported RBP and β2M levels to be highly correlated when urinary pH > 6.0, with progressively increasing RBP/β2M ratios as urinary pH declined, reflecting RBPs stability in acidic urine when compared with the instability of β2M.[21]

Cystatin-C

Serum concentrations appear to be independent of sex, age, and muscle mass. Cys-C is freely filtered by the glomerulus, reabsorbed and catabolized, but not secreted, by the tubules. Over the past decade, serum Cys-C has been extensively studied Vaidya et al. and found to be a sensitive serum marker of GFR and a stronger predictor than serum creatinine of risk of death and cardiovascular events in older patients.[21]

Kidney Injury Molecule-1

Kidney injury molecule-1 (KIM-1) is a type I cell membrane glycoprotein containing a unique six-cysteine immunoglobulin-like domain and a mucin domain in its extracellular region. KIM-1 mRNA levels increase more than any other known gene after kidney injury.[21]

Clusterin

Clusterin is induced in the kidney and urine of rats, dogs, and primates after various forms of preclinical AKI such as ischemia/reperfusion injury, toxicant-induced kidney injury, unilateral

ureteral obstruction, or subtotal nephrectomy.[21]

Urine IL-18 levels were significantly increased in patients with AKI compared with prerenal azotemia, urinary tract infection, chronic renal insufficiency, and nephrotic syndrome. Urinary IL-18 levels had sensitivity and specificity of 90% for diagnosis of established AKI in humans.[22]

MANAGEMENT OF ACUTE KIDNEY INJURY

AKI is a global problem with varying etiologies and manifestations, but the outcomes are similar. Given the wide global variation in the natural history and management of AKI, it is essential that mechanisms for sharing information and for collaboration among centers be developed. Having a standard for diagnosing and classifying AKI would enhance the ability to improve the management of these patients.[23]

The evaluation and initial management of patients with acute kidney injury (AKI) should include:

1) An assessment of the contributing causes of the kidney injury.
2) An assessment of the clinical course including comorbidities,
3) A careful assessment of volume status, and
4) The institution of appropriate therapeutic measures designed to reverse or prevent worsening of functional or structural kidney abnormalities.[24]

General supportive measures include optimisation of hemodynamic status by appropriate fluid therapy, administration of vasopressors and/or inotropes and treatment of any underlying sepsis. Nephrotoxic medications should be stopped. There is no specific pharmacological therapy proven to effectively treat AKI secondary to hypoperfusion injury and/or sepsis.[13]

Early in the course of AKI, optimization of the hemodynamic status and correction of any

volume deficit will have a salutary effect on kidney function, will help minimize further extension of the kidney injury, and will potentially facilitate recovery from AKI with minimization of any residual chronic impairment of kidney function.[24] However a positive fluid balance after the development of AKI is associated with increased mortality, as well as progression to more severe grades of AKI and increased requirement for renal support.[25]

Patients with AKI receiving renal replacement therapy (RRT) should be referred to a dietician for individual assessment. They should receive 25-35 kcal/kg/day and up to a maximum of 1.7g amino acids/kg/day if hypercatabolic and receiving continuous renal replacement therapy. Trace elements and water soluble vitamins should be supplemented as required.[13]

Interventions to enhance renal blood flow and decrease tubular reabsorption seem to be a logical approach for the prevention of outer medullary hypoxic injury. Loop diuretics block the active sodium-potassium-chloride co- transport in the apical membrane of the thick ascending limb renal tubular cells. The loop diuretic frusemide has been shown to reduce medullary demand by inhibiting solute reabsorption and to attenuate the severity of acute renal injury in animal models. It is postulated that it may protect the human kidney from ischaemic injury.[26]

In critically ill patients with acute renal failure, there is no evidence to suggest that the use of loop diuretics reduces mortality, reduces length of ICU/hospital stay, or increases the recovery of renal function.[26]

Several randomized clinical trials have explored the use of diuretics in established ARF and have not shown benefit in survival or recovery of renal function. Possible explanations for the associations observed include a direct toxic effect of diuretics or indirect effects either related or unrelated to renal function.[27] The choice of renal replacement therapy modality should be guided by the individual patient's clinical status, medical and nursing expertise, and

availability of modality.[13]

ACUTE KIDNEY INJURY IN SNAKE BITE PATIENTS

Snake venom is well known to cause toxic damage to the kidneys (Schreiner and Maher, 1965).[15] Published data suggest that the patient's age and body surface area, the snake's age, amount of inoculated venom, bite site and the time elapsed until anti-venom treatment all influence AKI prevalence.[8]

There is a wide range of renal manifestations in snakebite patients. In addition to local and systemic manifestations, clinical renal findings range from mild proteinuria, pigmenturia, hematuria to acute renal failure. Bites by hemotoxic and myotoxic snakes bites are the common causes of acute kidney injury.[28]

Upto 90% of the approximately 1000 deadly snake bites occurring per annum are attributed to Russell's Viper which is also the 5th most common cause of ARF in Burma. In Thailand 70% of ARF causes have been ascribed to Russell's viper envenomation. In India ARF is mostly associated with Russell's viper and E. cariatus bites and the incidence of ARF is 13-32%.[30]

Renal failure is the major cause of bite in viper bite. The possible mechanism of ARF are prolonged hypotension, DIC, intravascular hemolysis, nephrotoxicity of the venom and myoglobinuria.[33]

Acute renal failure is mainly observed following bites by the viperidae group but less with sea snakes and the colubridae group. Most Indian patients are victims of russells viper or Echis carinatus biites, causing ARF.[29]

CLINICAL RENAL MANIFESTATIONS

Proteinuria, acute renal failure and hematuria are the common renal manifestations in snakebite.

The incidence of acute renal failure following poisonous snakes varies from 13-22% following E.carinatus or Russell's viper bite. In most cases, the renal failure is attributed to tubular necrosis and cortical necrosis, though necrotizing interstitial and nephritic syndromes have also been reported.[32]

Proteinuria

Proteinuria may be observed following snakebite. It is less common and depends on the type of snake and geographical location. In a study of four hundred tropical snakebite patients it was observed only in four percent patients. The amount of proteinuria is less than five hundred milligram per day, and this is usually a transient finding which resolves completely with prompt treatment. Rarely nephrotic syndrome is seen in snakebite patients but the exact pathogenesis is not clearly understood.[28]

Hematuria

Hematuria is frequently associated with vaculotoxic snakebite, either viperid or crotalid snakes because of hemorrhagic diatheses, and it can be either microscopic or gross hematuria depending upon the degree of envenomation. Rarely, nephritic syndrome is observed in viper bite with pathological changes like crescentic and diffuse proliferative glomerulonephritis.[28]

Pigmenturia:

In viperid and crotalid snake bites Intravascular hemolysis is frequently seen. Therefore, in vasculotoxic snake bites hemoglobinuria is commonly observed. RBC swelling precedes

hemolysis with the rise in packed cell volume. Myoglobinuria may result from rhabdomyolysis due to the action of phospholipase A2 (present in myotoxic snake venom) on skeletal muscle. Hemoglobin and myoglobin in urine plays a major role in the pathogenesis of AKI in snake bite patients.[28]

Acute kidney injury

Either myotoxic or vasculotoxic snake bites cause acute acute kidney injury due to rhabdomyolysis, intravascular hemolysis, disseminated intravascular coagulation (DIC) or hemorrhage. Acute kidney injury in snakebite constitutes one percent of total AKI in Thailand, three percent in India, and seventy in Myanmar. After the bite, the onset of AKI may take few hours to days. Loin tenderness may be present. Low blood pressure is associated with AKI most of the times but transient increase in blood pressure is also observed. Along with intravascular hemolysis or disseminated intravascular coagulation renal failure may also present in viper bite. Hemoglobinuria and hematuria are also seen. Hemolytic uremic syndrome has been seen following hemotoxic snake envenomation. In myotoxic snakebite renal failure is associated with muscular pain, weakness, myoglobinuria and high serum creatine phosphokinase due to rhabdomyolysis. In both instances hyperkalaemia may be of an alarming degree.[28]

Acute kidney injury lasts for an average of two to three weeks duration. The duration of AKI increases if the patient has cortical necrosis or acute tubular necrosis associated with either interstitial nephritis or extracapillary glomerulonephritis. Mild renal failure can occur due to acute glomerulonephritis in viper bite. Except for those with cortical necrosis all other patients usually recover completely. Mortality of snake bite patients with AKI vary from one to twenty percent. Poor prognosis is seen in the elderly and those with cortical necrosis or severe hemorrhagic

complications.[28]

MANAGEMENT

Specific anti snake venom treatment is required and this should be given before AKI onset. Monovalent ASV is preferred. Plasmapheresis and hemodialysis have been used in snake bite patients where ASV is not available. But it is difficult because it has to be performed early before the venom attaches to the tissue.

Peritoneal dialysis or hemodialysis is lifesaving. Hemodialysis improves muscular symptoms in sea snakebite and suggests that it corrects high serum potassium and removes neurotoxin with low molecular weight.[28]

Renal failure should be prevented. Proper treatment with specific antivenom is required. Maintenance of good urine output is necessary. Alkalization of urine by sodabicarb helps in the prevention of AKI in the patients with haemoglobinuria or myoglobinuria if this is done early when urine is dark or the snake is known to be myotoxic or haemotoxic.[28]

In established AKI, administration of sodabicarb and mannitol is contraindicated due to volume overload and increased osmolality. Administration of furosemide and dopamine have shown to reduce the renal impairment in animal models of Russell's viper envenomation at early stage.[28]

RENAL PATHOLOGY

All kidney structures can be involved in snake envenomation

Glomerular changes

Glomerular involvement in snakebite is usually overlooked. Lysis of the mesangium is the early feature of glomerular involvement. In some patients mesangial proliferation of glomeruli has been observed following Russell's viper bite.

There is disintegration of the mesangial matrix. Proliferation of mesangial cells appears later, as a result of healing reaction. In humans, mild mesangial proliferative glomerulonephritis has been observed following the bite of Russell's viper, cobra, green pit viper and Habu snake.[28]

Tubulointerstitial changes

Necrosis, degeneration, and regeneration of tubular epithelial cells of the kidney following the bite by haematotoxic or myotoxic snakes have been observed. These changes can occur in any part of the renal tubule.

Interstitial oedema and cellular infiltration are also observed. Acute diffuse interstitial nephritis has been observed in Russell's viper bite. Also, there is diffuse and intense interstitial infiltration with mononuclear cells out of proportion to tubular degeneration.[28]

Changes in the blood vessels

Necrotizing inflammation of the interlobular arteries has been observed in Russell's viper bite. Following Russell's viper bite inflammation of arcuate vein and its branches has been observed.[28]

Cortical necrosis And Renal infarction

In studies on animals shown that renal infarction has been observed following pit viper snake venom administration.

In human, hemorrhagic infarct has been observed in the patients bitten by Russell's viper and rattlesnake. Fibrin platelet thrombi appears in interlobular arteries within or near the infarcted areas. Necrotic tubules containing hemoglobin casts are demonstrable.

The lesion is also associated with disseminated intravascular coagulation.Thrombi in the

renal vascular bed leads to necrosis of all elements of kidney. Calcification of the renal cortex with residual impairment of kidney function is noted in radiography of the recovered patients.[28]

PATHOGENESIS

The mechanism of renal failure in snakebite is complex involving 1) the inflammatory effects due to the release of various endogenous cytokines and mediators and 2) the direct effect of venom on the nephrons of the kidney. Vasoactive mediator release after viper snake bite, the concentrations of NE, epinephrine, dopamine, TX B2, endothelins and 6 keto Prostaglandin F α in plasma were elevated. The effects of cytokines and vasoactive mediators are reflected by the hemodynamic changes and immune response.

Snake venom poisoning has the same inflammatory process as infection or sepsis with the roles of cytokines, mediators, complement activation, reactive oxygen species and immunologic reaction.[28]

However, a number of factors may contribute to AKI viz. bleeding, hypotension, circulatory collapse, intravascular hemolysis, disseminated intravascular coagulation, microangiopathic hemolytic anemia.

Hypotension

Bleeding either into tissues or externally and loss of plasma into the bitten extremity can produce hypotension and circulatory collapse. This is caused by venom metalloproteinases. Additionally, vasodilatation and increased capillary permeability, both as a result of direct and indirect effects of venom, can aggravate the circulatory disturbances of shock. Irrespective of the cause, hypotension and circulatory collapse set in motion a chain of hemodynamic disturbances, which are known to culminate in ischemic ARF.[30]

Intravascular hemolysis[30]

Another factor thought to have pathogenetic significance in snake-bite- induced ARF is intravascular hemolysis. Hemolysis results from the action of phospholipase A_2 which is present in almost all snake venoms, and a basic protein called "direct lytic factor", found only in elapid venoms. Phospholipase A_2 causes hemolysis by 1) hydrolysis of RBC membrane or 2) via the synthesis of the strongly hemolytic lysolecithin from plasma lecithin. Evidence of intravascular hemolysis in the form of anemia, reticulocytosis, jaundice, raised plasma free hemoglobin, abnormal peripheral blood smear, and hemoglobinuria is seen in about 50% of patients following bites by the Russell's viper and E. carinatus.

Some have even suggested that renal failure following snake bite should be considered an example of the hemolytic uremic syndrome. However, while intravascular hemolysis is frequently observed, microangiopathic hemolysis as seen in hemolytic uremic syndrome is encountered only rarely. Moreover, more than 70-80% of patients with snake bite induced renal failure have only acute tubular necrosis and do not exhibit the glomerular and arteriolar changes characteristically associated with the hemolytic uremic syndrome.

Disseminated intravascular coagulation[30]

The human hemostatic system is regulated via a number of critical interactions involving blood proteins, platelets, endothelial cells, and sub- endothelial structures. Snake venom proteins and peptides are known to activate or inactivate many of these interactions. Snake venoms, particularly those from the viper and pit viper families, contain many proteins that interact with members of the coagulation.

Russell's viper venom (RVV) contains a factor V-activating serine proteinase, which has been separated from a factor X-activating protein, also present in this venom. The enzyme (RVV-V) is a single chain glycoprotein with a molecular weight of 26,100 possessing one glycosylation site near the carboxy terminus. RVV-V cleaves a single peptide bond to convert factor V to factor V_a (the activated clotting protein). Russell's viper venom also contains a potent activator of human coagulation factor X; this enzyme has been well characterized and is designated as RVV-X. Russell's viper venom also activates factor IX by cleavage of a single peptide bond resulting in the formation of factor IX_a.

There are several different types of prothrombin activators in snake venom. The activity of members of group I is not influenced by components of the prothrombin activator complex (factor V_a, CaCl2 and phospholipid). Ecarin, from E. carinatus venom, is the most well studied member of this group. Group II activators resemble factor X_a and can cleave both peptide bonds in prothrombin, leading to active 2-chain thrombin. Their activity is strongly stimulated by phospholipids and factor V_a in the presence of $CaCl_2$. By contrast, activators in group III require only phospholipid and $CaCl_2$ for the activation of prothrombin. They do not require factor V_a, but appear to possess a co-factor that is tightly bound to the catalytic subunit that plays a similar role to factor V_a in prothrombin activation. Although thrombin has many activities, the ability of some snake venom enzymes to clot fibrinogen has resulted in these enzymes being called “thrombin- like”. These are widely distributed primarily in the venom of snakes from true vipers and pitvipers. Snake venom fibrinogen clotting enzymes have been classified into several groups based on the rates of release of fibrino peptides A and B from fibrinogen.

One mechanism of the anticoagulant action of snake venom proteins is attributed to the activation of

protein C. Activated protein C degrades factors Va and VIIIa and therefore, has anticoagulant activity. Another mechanism of anticoagulation involves inhibition of blood coagulation factors IX and X by a venom protein(s) that binds to either or both. Finally, anticoagulation is also achieved through the action of snake venom phospholipases that degrade phospholipids involved in the formation of complexes critical to the activation of the coagulation pathway.

Direct-acting fibrinolytic enzymes have also been isolated from the venom of a number of North and South American snakes, including rattlesnakes and copperheads, and from elapids, including cobras and European vipers. The venom fibrinolytic enzymes that have been characterized in detail are zinc metalloproteinases and may be classified as either α or β chain fibrinogenases. Snake venoms also contain a number of platelet active components, including those that cause platelet aggregation and those that inhibit platelet aggregation. Renal failure is an important complication of snake bite and a major cause of mortality. Prevalence of thrombocytopenia (<150,000 K/UL) was 60% in AKI group and 40% in the non AKI group.[31]

The final coagulation disturbance depends upon the balance among the activity of procoagulant, anticoagulant, fibrinolytic and fibrinogenolytic components of injected venom. Disseminated intravascular coagulation (DIC) is a consistent feature in patients bitten by Russell's viper, E. carinatus, boomslang and pit vipers.

The occurence of fibrin thrombi in the renal microvasculature and in the glomerular capillaries, and the findings of microangiopathic hemolytic anemia and thrombocytopenia in patients with cortical necrosis strongly suggest that DIC plays a major pathogenetic role in snake-bite induced cortical necrosis. Snake venom initiates a chain reaction involving the coagulation, fibrinolytic, kinin and complement systems. Venom-induced alterations lead to vascular coagulation and to deposition of fibrin thrombi in blood vessels. These changes occur in patients as well as in experimental models.

Intraglomerular fibrin deposition of lesser degree has been suspected as causing acute tubular necrosis via a temporary hemodynamic alteration.

Direct nephrotoxicity[28]

Renal failure has been observed in patients a few hours after snakebite without hypotension, hemorrhage, intravascular hemolysis and rhabdomyolysis. The clinical evidence suggests direct nephrotoxicity of the venom. Mesangiolysis, glomerulonephritis and vasculitis without immunologic clues indicate direct glomerular and vascular injury by the venom. Venomous snakes have enzymes that can directly cause cellular injury.

Metalloprotease can cause proteolysis of the extracellular matrix and disrupts cell-matrix and cellular adhesion. The enzymes are present in the venoms of snakes in the Viperinae and Crotalinae subfamilies, and bind with various degrees of specificity to integrin alpha 4 ,beta 1, alpha 4, beta 7, alpha 5, beta 1, alpha 6, beta 1, alpha 9,beta 1,alpha V,beta 3,and alpha V, beta 5, expressed on cells.

Integrity of cellular junctions is disrupted as a result of disruption of the actin cytoskeleton resulting in a loss of cell polarity. Integrins which are critical for cellular adhesion, redistribute away from the basal cell surface, contributing to the loss of adhesion to the basement membrane. Metalloproteases can induce apoptosis of vascular endothelial cells.

Phospholipase A2 enzymes are present in several poisonous snakes including crotalids, viperids, elapids and hydrophids. The enzymes are toxic and induce a wide spectrum of pharmacological effects. Phospholipase A2 can cause membrane injury and tubular necrosis. The enzymes interact with the biological membranes via a distinct molecular region. This active region

is most likely to be formed by the interaction of basic hydrophobic amino acids with the C-terminal end of the protein. The high affinity interaction of PLA2 with its target protein is probably due to the interaction of charges, hydrophobicity and van der Waal's contact surfaces between the toxin and the binding site as the surface of the cell membrane. These events lead to membrane destabilization and loss of permeability and cellular necrosis.

Immunological mechanism[28]

Immunologic mechanisms play a minor role in the pathogenesis of glomerulonephritis. In contrast to glomerulonephritis seen without immunologic evidence in acute animal experiments and in a number of patients bitten by snakes, immune complex glomerulonephritis has been observed later in the course of snakebite regardless of antivenom administration. There is deposition of C3 and IgM in the glomerular mesangium. The evidence suggests an immune complex glomerulonephritis with implanted antigen, followed by IgM deposit acquired naturally.

Alternatively, this could be due to a concealed infection in the snakebite that results in immune complex glomerulonephritis with predominant deposition of IgM and C3 in the mesangial areas. At present, the evidence is in favour of glomerulonephritis directly induced by the snake venom. The immunological role is rather weak but cannot be entirely denied, especially the role of immune complex insitu.

Snake-bites are well known medical emergencies in many parts of the world, especially in rural areas. Agricultural workers and children are the most affected. The incidence of snake-bite mortality is particularly high in South-East Asia. Rational use of snake anti-venom can substantially reduce mortality and morbidity due to snake bite.

Cerebral infarction is rare and there are only few case reports all over world.

Snake venom is a complex fluid. Main components of snake venom are protease, collagenase and

phospholipases, which are responsible for local swelling, tissue destruction, vascular damage, alteration of coagulation profile and neurotoxicity. Most of the viper venom exhibit both anticoagulant and coagulant effects. As a procoagulant it has thrombin like activity, can activate prothrombin even in the absence of calcium ion, activate factor x and v and endothelial cells. Features of viper bite depend on severity of envenomation and bleeding manifestations are commonly encountered in the clinical practice. Thrombotic manifestations are uncommon. Large doses of venom can produce massive intravascular clotting with ischemic sequelae of major organs.[31]

In a prospective study in Sri Lanka on 500 victims of D. russelii bites, 9 patients (1.8%) have CT evidence of ischemic strokes involving medium to large vessel territories of the brain. According to this study, pro thrombotic property of the viper venom was the putative mechanism.[3]

There are several mechanisms by which cerebral infarction can occur in viper bite.

1) Hypotension, which can cause watershed infraction. Hypotension can be due to excessive sweating, vomiting, and increased vascular permeability due to release of vasogenic agents or adrenal hemorrhage.

2) Endothelial injury by direct action of components of viper venom on vessel wall may produce vasculitis and local thrombosis.

3) Hypercoagulability - it can be due to procoagulants in the venom such as arginine, esterase, hydrolase, hyper viscosity due to hypotension,

4) Vascular - hemorrhaging are complement mediated toxic components of viperidae that causes severe vascular spasms followed by vasodilatation, while at capillaries they cause increased vascular permeability, resulting in hemorrhagic infarct.[38,39]

The pathogenesis of CLS is not fully elucidated. Some protein components of the viper venom are thought to cause systemic vascular endothelial damage. Vascular permeability increases as a result of endothelial damage, leading to leakage of plasma to interstitial space and edema formation, hypoalbuminemia, and intravascular volume depletion. Two vascular apoptosis-inducing proteins (VAPs) from snake venom which are members of the metalloproteinase/disintegrin family have already been described. VAP1 is a basic, homodimeric protein with a molecular mass of 110 kDa, and VAP2 is an acidic, monomeric protein with a molecular mass of 55 kDa.[40]VAP2 has been shown to kill vascular endothelial cells in culture, and the death of cells exhibited the characteristic features of apoptosis. The apoptotic activity of VAP2 seemed to be specific to endothelial cells.[40] A 110 kDa enzyme called L-amino acid oxidase is another apoptosis-inducing factor isolated from hemorrhagic snake venom.[41,42]

There are no accepted diagnostic criteria. They suggest the criteria used by Thomas and Kumar with some modifications.[43] Diagnosis is made in the presence of bilateral parotid swelling, chemosis, and periorbital edema following snakebite along with any three or more of the following:

• Systolic blood pressure 45% or >20% elevation from the baseline

• Proteinuria defined by protein-creatinine ratio >1

• Serum albumin <3 g/dl

• Sonological evidence of the third-space fluid collection.

Many patients following Russell's viper envenomation develop lesser degrees of periorbital puffiness and parotid edema than seen in typical CLS, without hypotension, which usually resolves in 2–3 days. This may be considered as a milder form of CLS not fulfilling all the necessary criteria of CLS.

METHODOLOGY

Source of Data

Patients with history of snake bite who fulfilled the inclusion and exclusion criteria, got admitted at Shri B M Patil Medical College, Hospital and Research Center, Vijayapura .

Study Design: Prospective Observational Study

Study Period: A duration of 2 years from August 2018 to August 2020

Sample size: 65

Sampling method: Simple random sampling

Inclusion Criteria

1. History of snake bite with signs of envenomation.
2. Progressive elevation of creatinine more than 0.3 milligram/decilitre from initial value, a % increase in creatinine value of more than 50 percent or urine output less than 0.5 millilitre/kilogram/hour for more than six hours.

Exclusion Criteria

Patients with pre-existing renal diseases with history of snake bite.

Patients with risk factors for developing renal disease with history of snake bite. (diabetes, hypertension, connective tissue diseases, chronic infection)

Data has been collected using a pretested proforma meeting the objectives of the study. Detailed history, physical examination and necessary investigations have been done. The purpose of the study has been explained to the patient and informed consent was obtained. Using non-invasive methods acute kidney injury in snake bite patients who fulfilled the inclusion criteria was assessed. Patients are classified into three stages of acute kidney injury

proposed by Acute Kidney Injury Network which defines AKI as a abrupt i.e within 48 hours absolute increase in the serum creatinine concentration of ≥0.3 milligram/decilitre from initial value, a % increase in the creatinine value more than and equal to fifty percent or oliguria of 0.5 milli litre/kilogram/hour >6 hours.

The course of acute kidney injury in three stages and need for renal replacement therapy was assessed.

INVESTIGATIONS

1. COMPLETE HEMOGRAM
2. WHOLE BLOOD CLOTTING TIME
3. BLEEDING TIME
4. BLOOD UREA
5. SERUM CREATININE
6. CREATINE KINASE
7. PROTHROMBIN TIME
8. PARTIAL THROMBOPLASTIN TIME
9. USG ABDOMEN

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" is the degrees of freedom. "O" is observed value and E is expected value. C= (number of rows-1)* (number of columns-1)

The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

The t statistic to test whether the means are different can be calculated as follows:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

where $\bar{x}_1$ = mean of sample 1

$\bar{x}_2$ = mean of sample 2

n_1 = number of subjects in sample 1

n_2 = number of subjects in sample 2

s_1^2 = variance of sample 1 = $\frac{\Sigma(x_1 - \bar{x}_1)^2}{n_1}$

s_2^2 = variance of sample 2 = $\frac{\Sigma(x_2 - \bar{x}_2)^2}{n_2}$

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant.

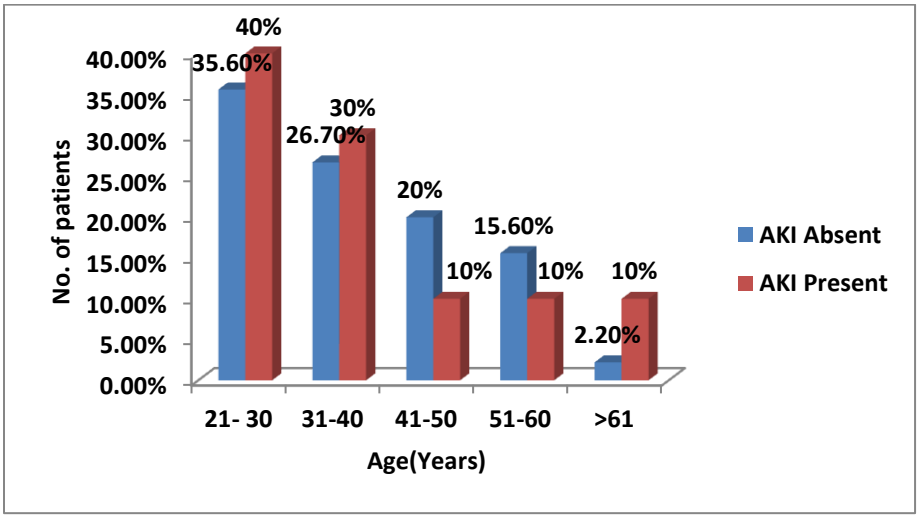
RESULTS:

A prospective clinical study was undertaken at Shri.B.M. Patil Medical College,Hospital and Research center, Vijayapura with 65 snake bite patients, who satisfied our inclusion and exclusion criteria to study the association of Acute Kidney Injury in snake bite.

Table no.1 ASSOCIATION BETWEEN AGE GROUP AND AKI

Age (Years)	AKI		TOTAL	Chi square test	P value
	ABSENT	PRESENT			
21- 30	16	8	24	X^2=3.071	P=0.581
%	35.6%	40.0%	36.9%		
31 - 40	12	6	18		
%	26.7%	30.0%	27.7%		
41 - 50	9	2	11		
%	20.0%	10.0%	16.9%		
51 - 60	7	2	9		
%	15.6%	10.0%	13.8%		
>61	1	2	3		
%	2.2%	10.0%	4.6%		
TOTAL	45	20	65		
Insignificant					

FIGURE 1: ASSOCIATION BETWEEN AGE GROUP AND AKI

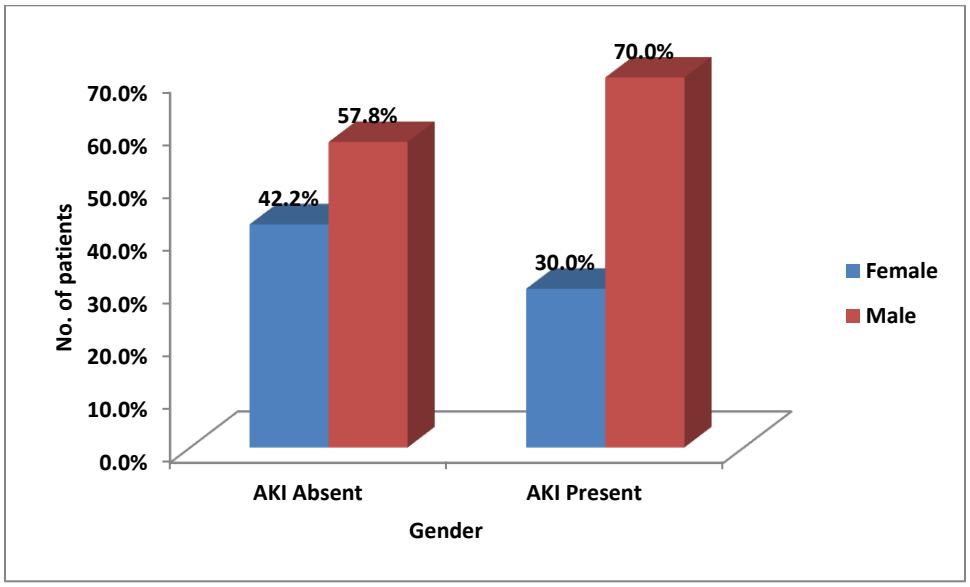


There is no statistically significant correlation between AKI and age group and in our study 24 patients were in the age group of 21-30 yrs out of which AKI was observed in 8 patients

Table no.2 Association between Gender and AKI

Gender	AKI		TOTAL	Chi square test	P value
	ABSENT	PRESENT			
Female	19	6	25	$X^2=0.874$	P=0.254
%	42.2%	30.0%	38.5%		
Male	26	14	40		
%	57.8%	70.0%	61.5%		
TOTAL	45(100)	20(100)	65(100)		
Insignificant					

FIGURE 2: Association between Gender and AKI

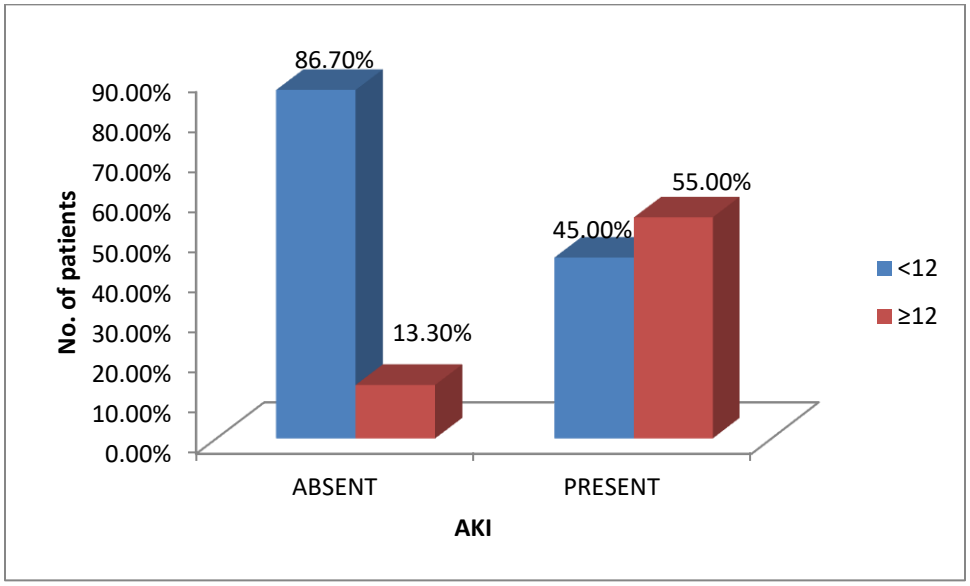


There is No Statistically Significant Correlation between Gender and AKI Out of 65 patients included in our study,40 were males in which AKI is observed in 14 patients

Table 3 : Association between Lapse of time in hours and AKI

Lapse of time in hours	AKI		Total	Chi square test	P value
	ABSENT	PRESENT			
<12	39	9	48	12.446	0.001*
%	86.7%	45.0%	73.8%		
≥12	6	11	17		
%	13.3%	55.0%	26.2%		
Total	45	20	65		
*:Highly significant					

Figure 3: Association between Lapse of time in hours and AKI

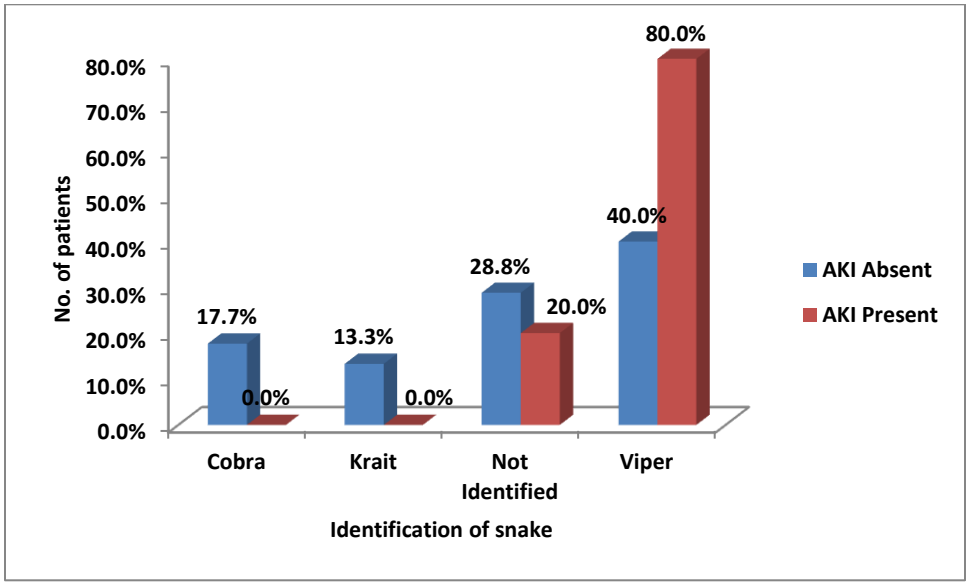


There is statistically significant correlation between AKI and lapse of time .55% of patients who presented with time lapse of >12hrs had AKI

Table 4: Association between Type of Snake Bite and AKI

Type of snake	AKI		TOTAL	Chi square test	P value
	ABSENT	PRESENT			
Cobra	8	0	8	X^2=12.821*	P=0.029
	17.7%	0.0%	3.1%		
Krait	6	0	6		
	13.3%	0.0%	9.2%		
Unknown	13	4	17		
	28.8%	20.0%	23.1%		
Viper	18	16	34		
	40.0%	80.0%	50.8%		
Total	45(100)	20(100)	65(100)		
*:Significant					

FIGURE 4: Association between Type of Snake Bite and AKI

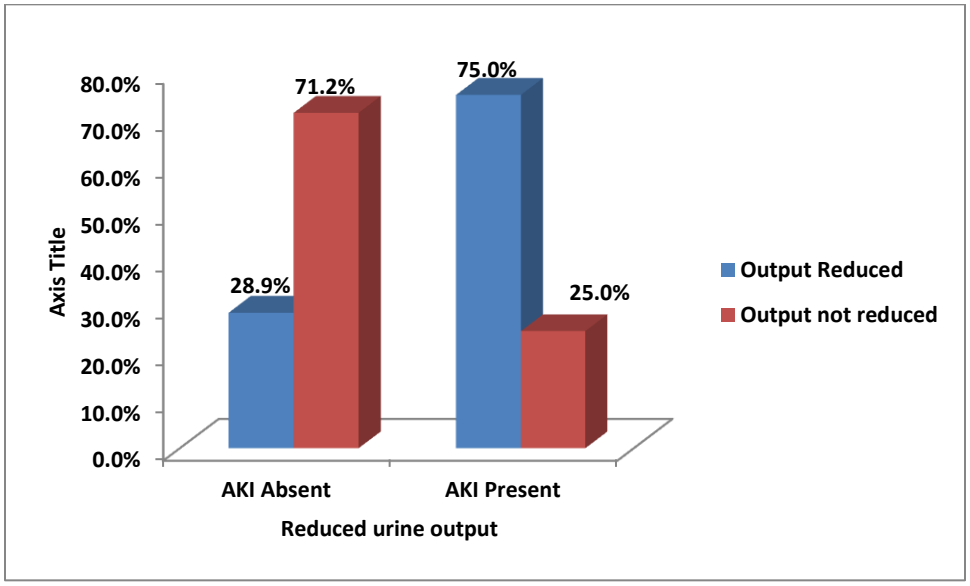


Statistically there is significant Correlation between AKI and type of Snake bite . In this study out of 20 patients with AKI , 16 patients (80% of AKI) was due to Viper Bite where as 4 patients(20% of AKI) was due to Unknown Snake bite .

Table 5: Association between reduced urine output and AKI

Reduced urine output	AKI		TOTAL	Chi square test	P value
	ABSENT	PRESENT			
Yes	13	15	28	X^2=18.614	P=0.001*
%	28.9%	75.0%	43.1%		
No	32	5	37		
%	71.2%	25.0%	57.0%		
TOTAL	45(100)	20(100)	65(100)		
*:Highly significant					

FIGURE 5: Association between reduced urine output and AKI



Statistically there is significant correlation between AKI and reduced urine output,In this study we have observed that urine output is reduced in 75 % of AKI patients.

TABLE 6: Association between hematuria and AKI

Hematuria	AKI		TOTAL	Chi square test	P value
	ABSENT	PRESENT			
Yes	13	15	28	X^2=4.312	P=0.042*
%	28.8%	75.0%	43.07%		
No	32	5	37		
%	71.2%	25.0%	56.92%		
TOTAL	45(100)	20(100)	65(100)		
*:Significant					

FIGURE 6: Association between hematuria and AKI

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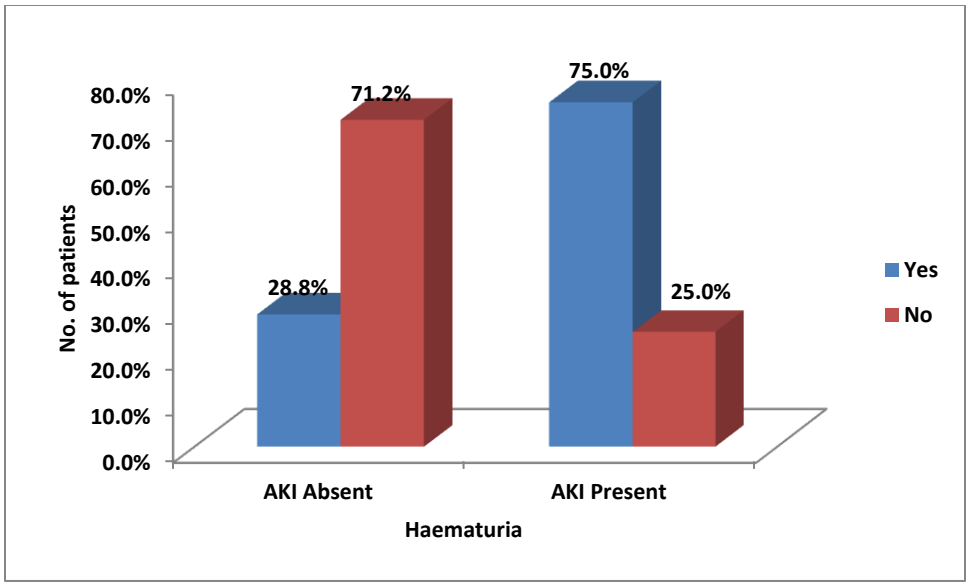
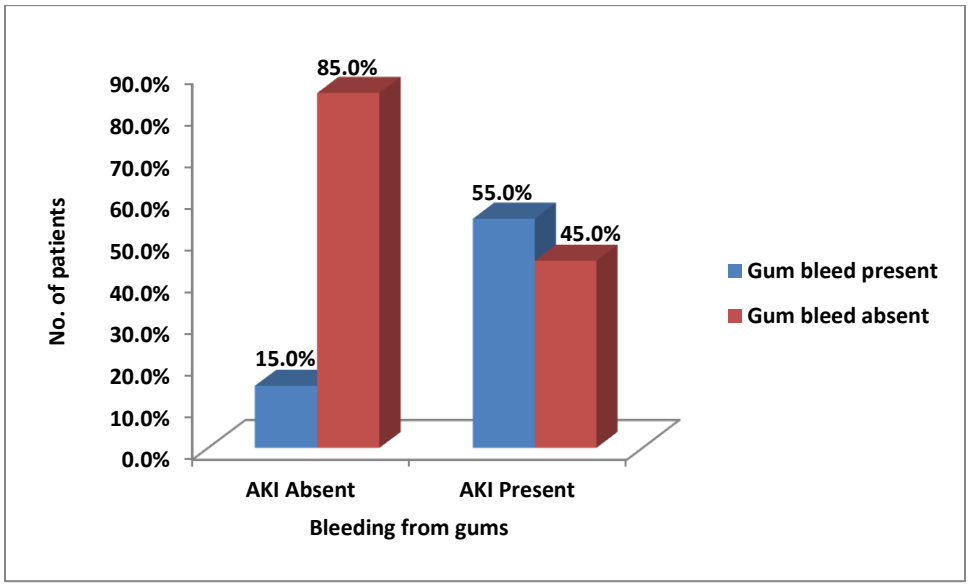


Statistically significant correlation is seen between presence of hematuria and AKI.In this study we have observed that 75% of AKI patients have hematuria.

TABLE 7: Association between Bleeding Gums and AKI

Bleeding from gums	AKI		TOTAL	Chi square test	P value
	ABSENT	PRESENT			
Yes	7	11	18	X^2=0.538	P=0.0362
%	15%	55%	27.69%		
No	38	9	47		
%	85%	45%	72.3%		
TOTAL	45(100)	20(100)	65(100)		
*:significant					

FIGURE 7: Association between Bleeding Gums and AKI

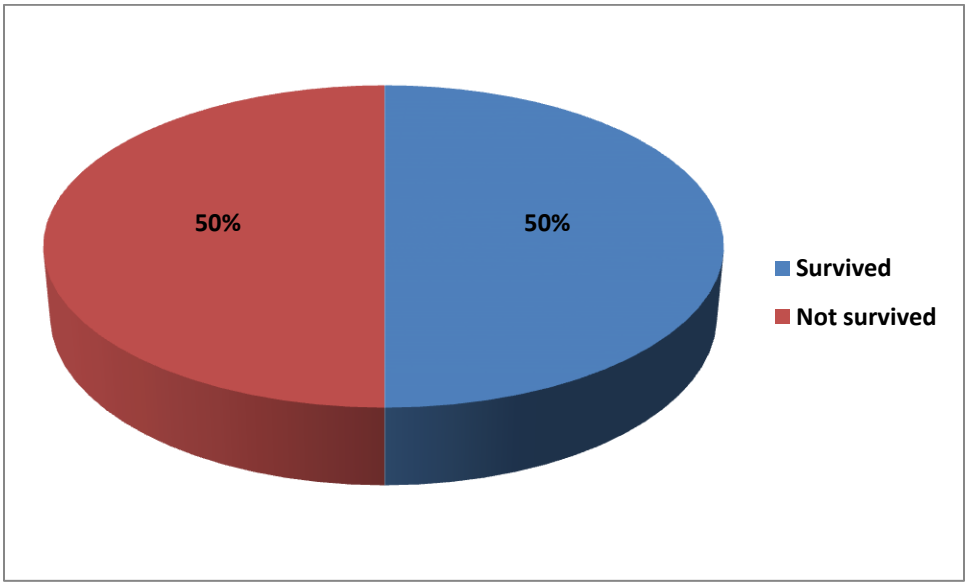


Statistically there is significant correlation between between AKI and Beeding Gums. In this study we have observed that 55% of AKI patients have Bleeding Gums

TABLE 8 In hospital outcome of patients who underwent Hemodialysis

In hospital outcome of patients who underwent hemodialysis	No. of patients	Percentage
Survived	3	50
Not survived	3	50
Total	6	100

FIGURE 8 In hospital outcome of patients who underwent Hemodialysis

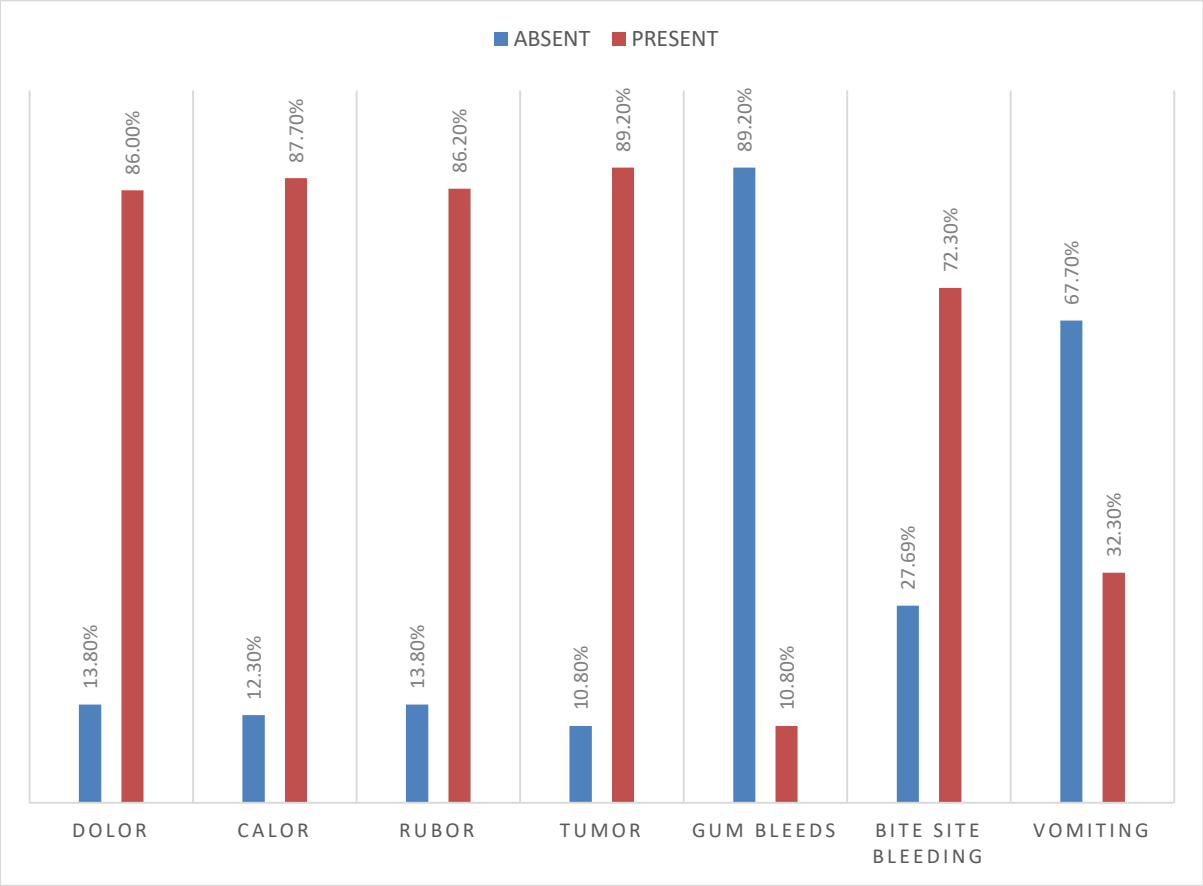


In this study it was observed that need for dialysis is seen in 6 patients (9%) out of 65 .Among 6 patients 3 patients were died and 3 patients survived.

TABLE 9: Clinical features of snake bite patients studied.

Parameters	No. of patients	Percentage
Clinical manifestations		
Signs of Inflamation		
Dolor		
Absent	9	13.8
Present	56	86.2
Calor		
Absent	8	12.3
Present	57	87.7
Tumor		
Absent	7	10.8
Present	58	89.2
Rubor		
Absent	9	13.8
Present	56	86.2
Bleeding from gums		
Absent	58	89.2
Present	7	10.8
Bleeding from bite site		
Absent	18	27.69
Present	47	72.30
Vomiting		
Absent	44	67.7
Present	21	32.3
Total	65	100.0

FIGURE 9 : Clinical Manifestations

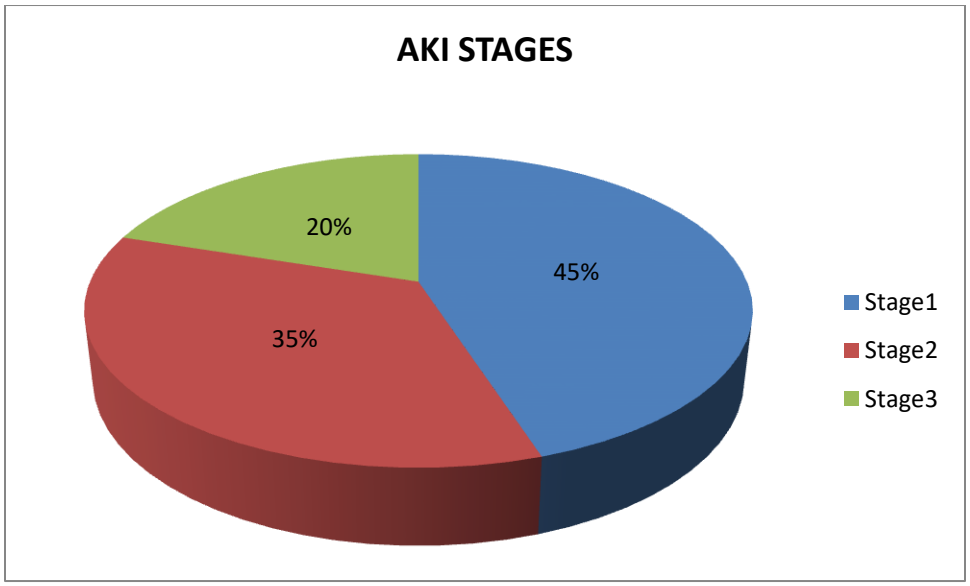


In this study it was observed that signs of inflammation like dollor,calor,rubor,tumour is observed in about 86 % cases,bleeding from site of bite is observed in 72 % cases,vomiting is present in 32.30% cases,gum bleed was observed in 10.80% cases.

TABLE 10: AKI STAGING in snake bite patients

AKI STAGING	Frequency	Percentage
1	9	45
2	7	35
3	4	20
Total	20	100.0

FIGURE 10: AKI staging

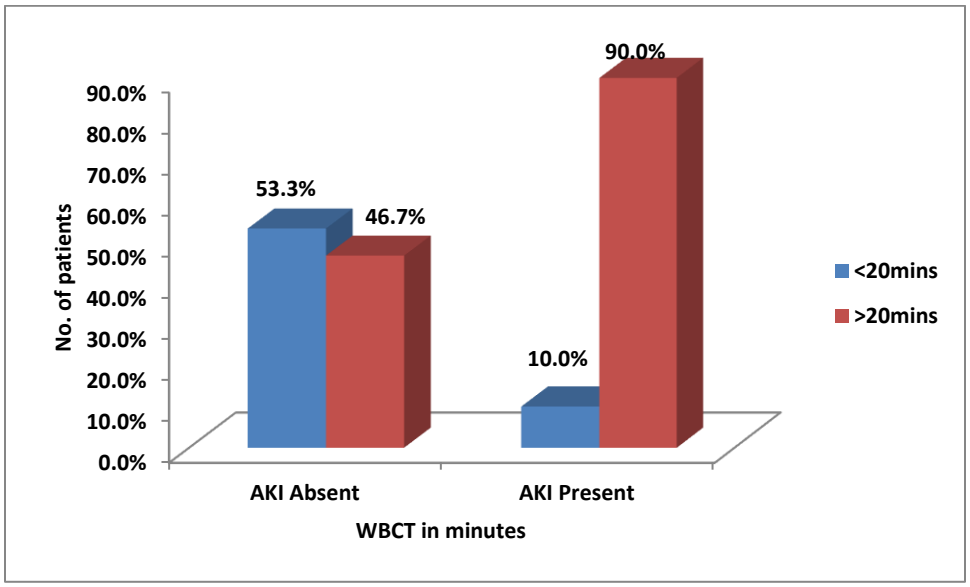


In this study AKI was present in 31% cases.Among AKI patients stage1=45%, stage2=35%,stage3=20%

TABLE 11: Association between 20 minute whole blood clotting time and AKI

		AKI		Total	Chi-Square	P Value.
		ABSENT	PRESENT			
wbct in minutes	<20	24	2	26	10.833	0.001
		53.3%	10.0%	40.0%		
	>20	21	18	39		
		46.7%	90.0%	60.0%		
Total		45	20	65		
		100.0%	100.0%	100.0%		

FIGURE 11: Association between 20 minute whole blood clotting time and AKI

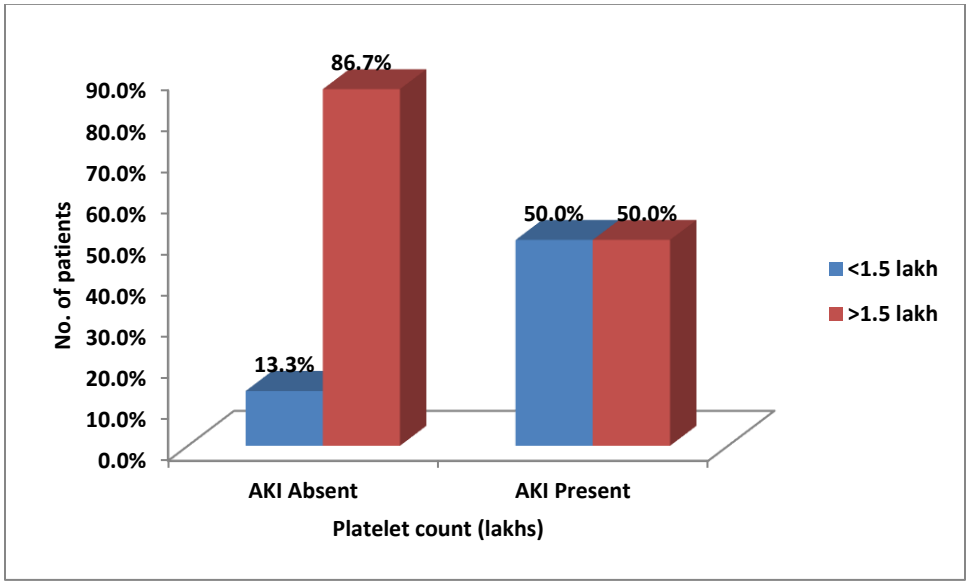


There is statistically significant correlation between AKI and 20 minute whole blood clotting time.In this study it was observed that 90% of AKI patients have whole blood clotting time >20 mins.

Table 12 : Association between platelet count and AKI

Platelet count (lakhs)	AKI		Total	Chi square test	P value
	ABSENT	PRESENT			
<1.5	6	10	16	10.032	0.003*
%	13.3%	50.0%	24.6%		
≥1.5	39	10	49		
%	86.7%	50.0%	75.4%		
Total	45	20	65		
*:Highly significant					

FIGURE 12 : Association between platelet count and AKI

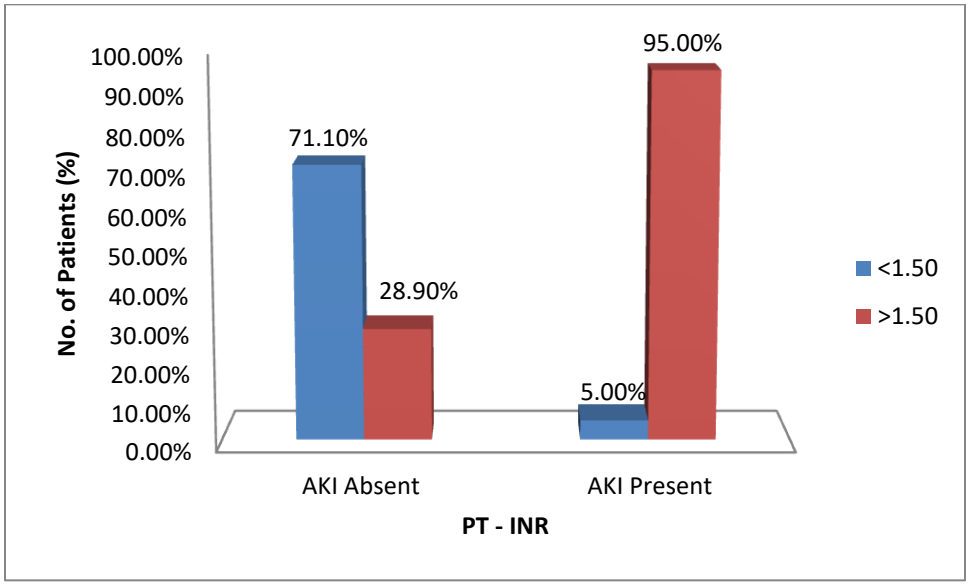


There is statistically significant correlation between AKI and platelet Count. In this Study We have observed that 50% of AKI patients had platelet Count less than 1.5 lakh.

TABLE 13: Association between PT-INR and AKI

		AKI		Total	Chi-Square	P Value.
		ABSENT	PRESENT			
PT-INR	< 1.50	32	1	33	24.213	0.001
		71.1%	5.0%	50.8%		
	1.50+	13	19	32		
		28.9%	95.0%	49.2%		
Total		45	20	65		
		100.0%	100.0%	100.0%		

FIGURE 13 : Association between PT-INR and AKI

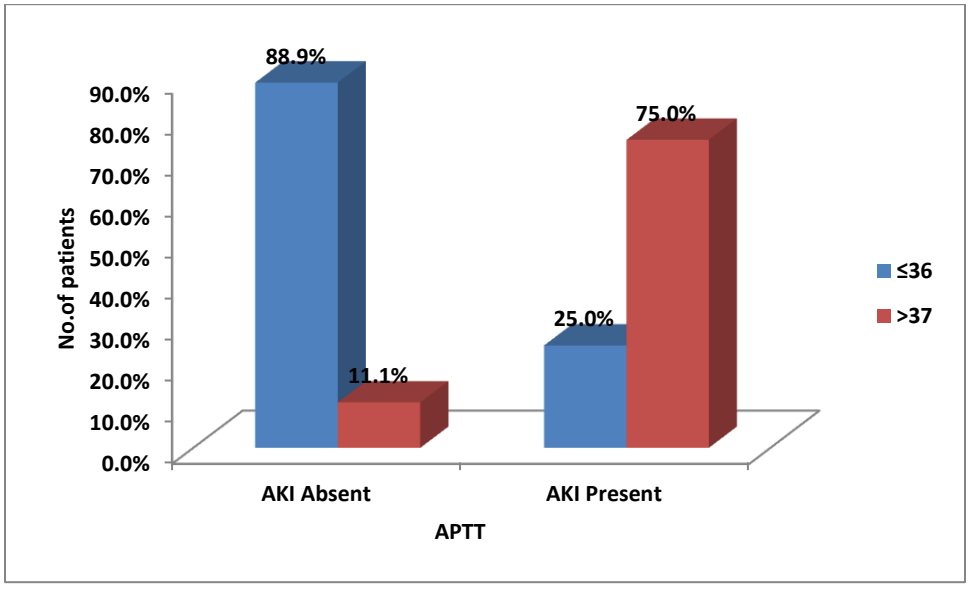


There is statistically significant correlation between AKI and PT-INR. In this Study it was observed that 95% of AKI patients had PT-INR more than 1.5 .

TABLE 14: Association between APTT and AKI

		AKI		Total	Chi-Square	P Value.
		ABSENT	PRESENT			
APTT	<= 36	40	5	45	26.532	0.001
		88.9%	25.0%	69.2%		
	37+	5	15	20		
		11.1%	75.0%	30.8%		
Total		45	20	65		
		100.0%	100.0%	100.0%		

FIGURE 14: Association between APTT and AKI

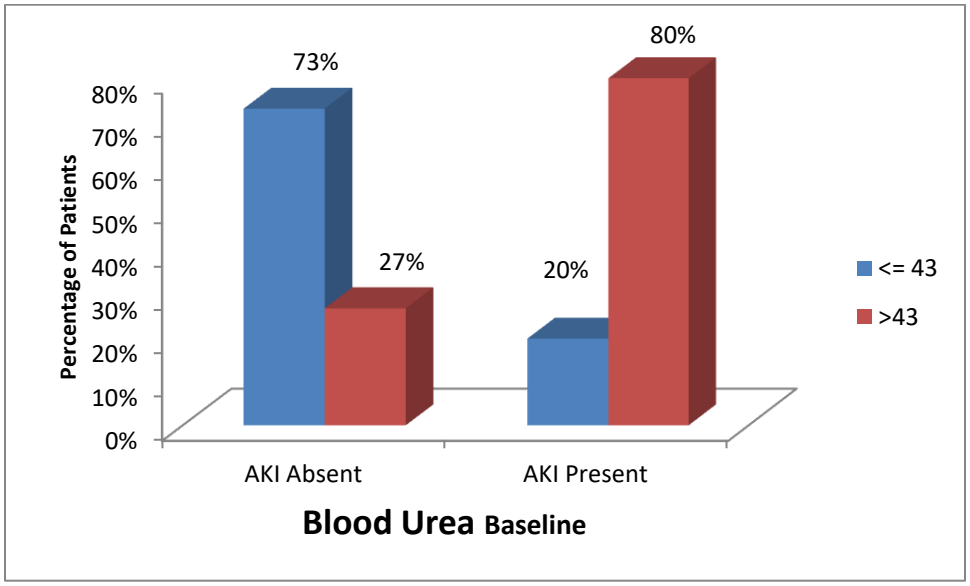


There is statistically significant correlation between AKI and APTT. In this Study it was observed that 75% of AKI patients had APTT more than 37.

TABLE 15a: Association between baseline Blood Urea and AKI

		AKI		Total	Chi-Square	P Value.
		ABSENT	PRESENT			
Blood urea	<= 43	33	4	37	17.984	0.001
		73%	20%	57%		
	>43	12	16	28		
		27%	80%	43%		
Total		45	20	65		
		100.00%	100.00%	100.00%		

FIGURE 15a: Association between baseline Blood Urea and AKI

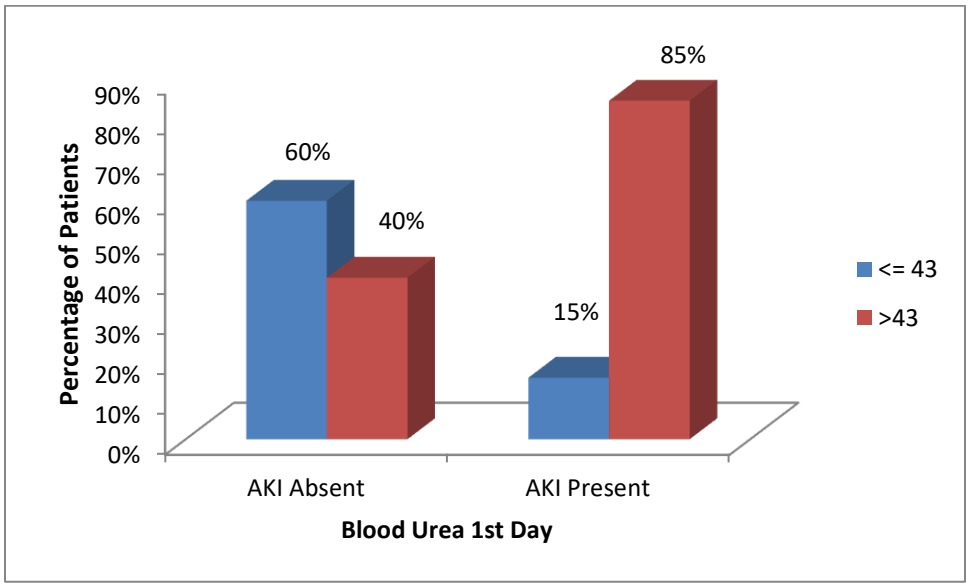


There is statistically significant correlation between AKI and blood urea. In this Study it was observed that 80% of AKI patients had blood urea more than 43 at baseline.

TABLE 15b: Association between Blood Urea at 24hrs and AKI

		AKI		Total	Chi-Square	P Value.
		ABSENT	PRESENT			
at 24 hrs	<= 43	31	2	36	20.526	0.001
		59.61%	15.38%	55.38%		
	>43	21	11	29		
		40.38%	84.61%	44.61%		
Total		52	13	65		
		100.0%	100.0%	100.0%		

FIGURE 15b: Association between Blood Urea at 24hrs and AKI

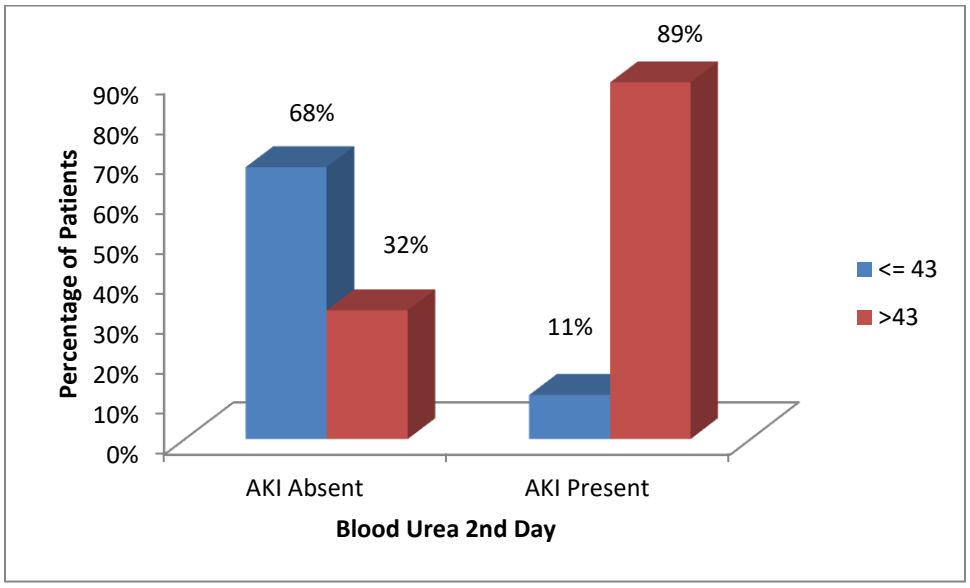


There is statistically significant correlation between AKI and blood urea at 24 hours . In this Study it was observed that 85% of AKI patients had blood urea at 24hrs more than 43 at baseline.

TABLE 15c: Association between Blood Urea on 2nd Day and AKI

		AKI		Total	Chi-Square	P Value.
		ABSENT	PRESENT			
2nd day	<= 43	38	1	39	26.340	0.001
		67.85%	11%	60%		
	>43	18	8	26		
		32.14%	89%	40%		
Total		56	9	65		
		100.0%	100.0%	100.0%		

FIGURE 15c: Association between Blood Urea on 2nd Day and AKI

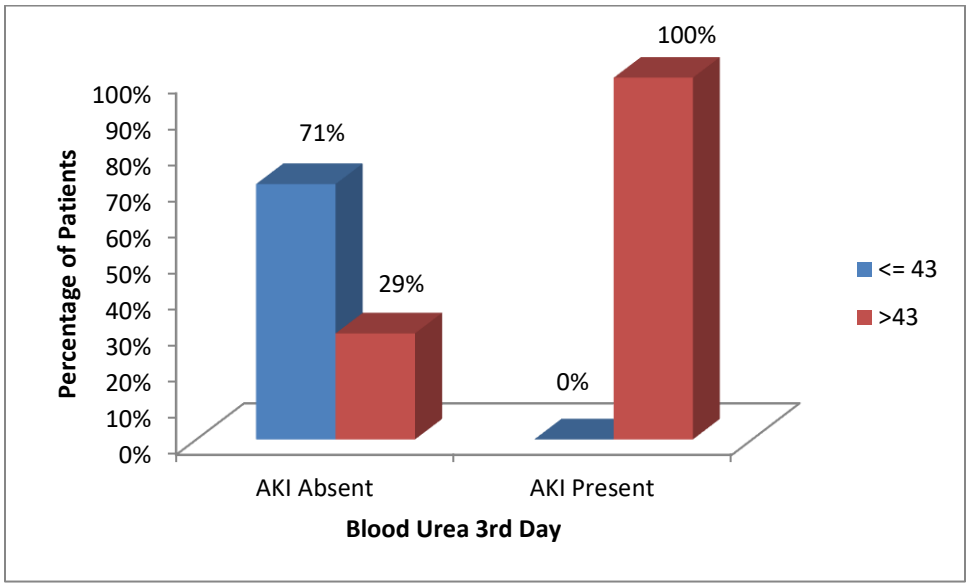


There is statistically significant correlation between AKI and blood urea at 2nd day. In this Study it was observed that 89% of AKI patients had blood urea more than 43 .

TABLE 15d: Association between Blood Urea on 3rd Day and AKI

		AKI		Total	Chi-Square	P Value.
		ABSENT	PRESENT			
3rd day	<= 43	41	0	41	22.803	0.001
		70.6%	0.0%	63.0%		
	>43	18	6	24		
		29.3%	100.0%	37%		
Total		59	6	65		
		100.0%	100.0%	100.0%		

FIGURE 15d: Association between Blood Urea on 3rd Day and AKI

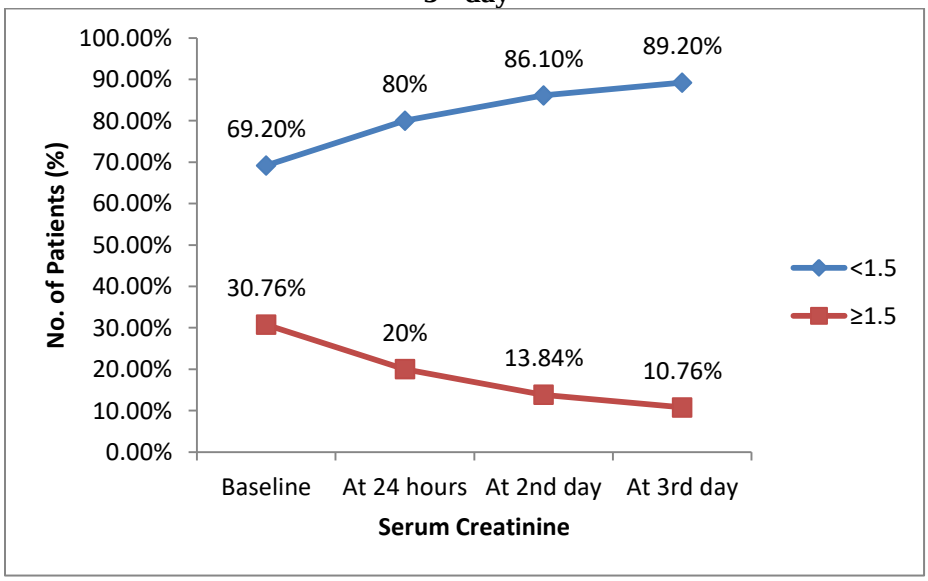


There is statistically significant correlation between AKI and blood urea at 3rd day. In this Study it was observed that 100% of AKI patients had blood urea more than 43.

Table 16: variation of serum creatinine values with respect to time at base line,24 hrs,2nt day and 3rd day

Serum Creatinine	<1.5 N (%)	≥1.5 N (%)	Chi-Square	P Value.
Baseline	45(69.2)	20(30.76)	22.803	0.001
At 24 hours	52(80)	13(20)		
At 2nd day	56(86.1)	9(13.84)		
At 3rd day	59(89.2)	6(10.76)		

Figure 16: variation of serum creatinine values with respect to time at base line,24 hrs,2nt day and 3rd day

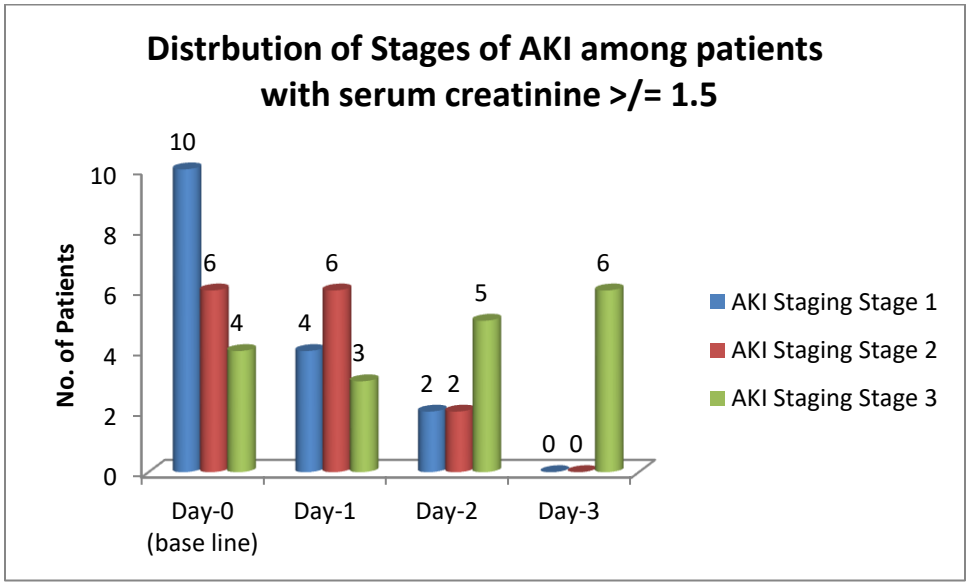


Number of patients having serum creatinine ≥1.5mg/dl at base line, 24 hrs,2nd day and 3rd day are 30.7%,20%,13.8% and 10.7% respectively.

TABLE 17: Distribution of Stages of AKI among patients with serum creatinine >/= 1.5

Distribution of Stages of AKI among patients with serum creatinine >/= 1.5				
	AKI Staging			
	Stage 1	Stage 2	Stage 3	**Total**
Day-0 (base line)	10(50%)	6(30%)	4(20%)	**20**
Day-1	4(31%)	6(46%)	3(23%)	**13**
Day-2	2(22%)	2(22%)	5(38%)	**9**
Day-3	0(0%)	0(0%)	6(100%)	**6**

FIGURE :17 : Distrbution of Stages of AKI among patients with serum creatinine >/= 1.5

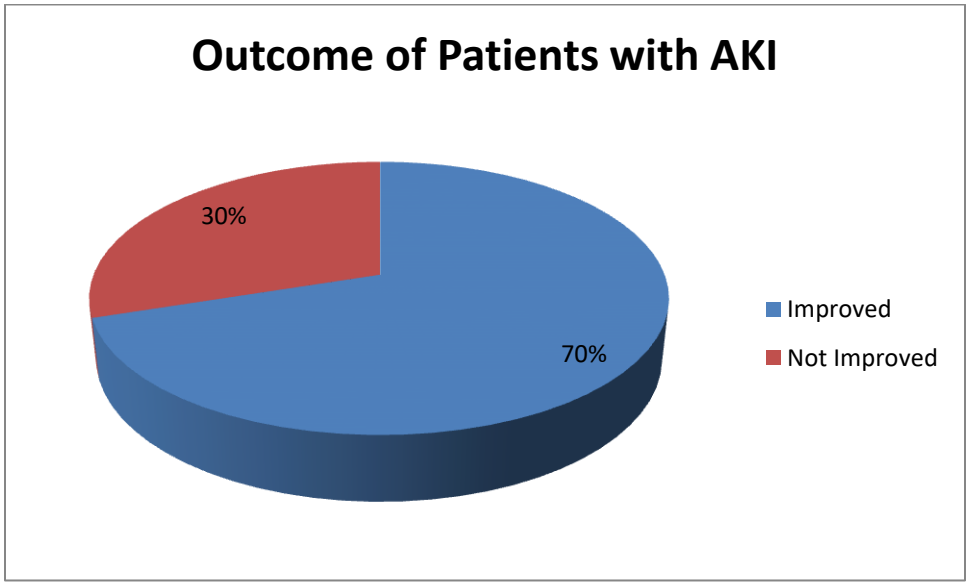


In this study we have observed that at base line percentage of patients of stage 1 ,stage 2,stage 3 respectively are 50%,30% and 20%.
On day 1:stage 1,stage 2,stage 3 respectively are 31%,46% and 23%.
On day 2: stage 1,stage 2,stage 3 respectively are 22%,22%,38%.
On stage 3: stage 1,stage 2,stage 3 respectively are 0%,0%,100%.

TABLE 18: In hospital outcome of Snake bite patients with AKI.

Outcome	Frequency	Percent
Not improved	6	30
IMPROVED	14	70
Total	20	100.0

FIGURE 18: In hospital outcome of Snake bite patients with AKI.



Out of 20(100%) patients with AKI, 13(65%) were improved and 7 (35%) were not improved.

DISCUSSION

In the present study, 65 cases were selected on the basis of simple random sampling method from the casualty and medical wards, Shri B.M Patil Medical College, Hospital and Research center, vijayapura who presented with history of snake bite .

1.Age distribution

Table 19: Comparison of age distribution with other studies

Studies	Mean age (years)of aki patients	SD
Paul J Dasgupta and others[34]	45.6	01.64
Patil BT and others[35]	36.8	14.92
Present study	32	13.3

In the present study mean age of AKI patient was 32.4 which is similar to Patil BT study which has a mean age of AKI 36.8 years but not similar with paul j dasgupta study which had a mean age of AKI 45.6 years.

2.Sex distribution

Table 20: Comparison of gender distribution in AKI patients with other studies

Studies	Male	Female
Athappan G and Others[29]	62.6%	37.4%
Mittal BV and Others[32]	58.53%	41.46%
Present study	70%	30%

In the present study, males patients with AKI account for 70% and females patients with AKI account for 30% which is similar to Athappan G study in which males patients with AKI accounts for 62.6% and female patients account for 37.4% patients but present study is not consistent with Mittal BV study in which males patients with AKI accounts for 58.5% and female patients with AKI accounts for 41.5%.

3.Lapse of time in hours

Table 21: Percentage of AKI patients with Lapse of time of >12 hours in presenting to the hospital

Studies	Percentage
Patil BT and others[35]	42%
Athappan G and Others[29]	52%
Present study	55%

In the present study 55% of AKI patients have lapse of time >12 hours which is consistent with athappan G study in which 52 % of AKI patients have lapse of time >12 hrs .Present study also consistent with Patil BT study in which 42% of AKI patients have lapse of time >12 hrs.

4.Symptoms

Table 22: Comparison of symptoms in AKI patients with other studies

Symptoms	Ath Athappan G and Others[29]	Present study
Reduced urine output	100%	75%
Bleeding from gums	10%	55%
Signs of inflammation	98.7%	86.2%

In the present study 75 % of AKI patients was associated with reduced urine output which is consistant with Athappan G study in which it was observed in 100% patients with AKI.
In the present study 55 % of AKI patients had Bleeding from gums which is not consistent with Athappan G study in which it was observed in only 10% of AKI patients.
In the present study 86 % of AKI patients have signs of inflammation which is consistent with Athappan G study in which it was 98.7% .

5.Coagulation profile

Table 23: Comparison of abnormal coagulation profile in AKI patients with other studies

Studies	Percentage
Patil BT and others[35]	36.8%
Mittal BV and Others[32]	73.17%
Present study	75 %

In the present study 75% of AKI patients with abnormal coagulation profile which was consistent with Mittal BV study in which it was 73.1% but it was not consistent with Patil BT study in which it was only 36.8%.

6. Whole Blood Clotting Time (WBCT)

Table 24: Comparison of WBCT >20 mins in AKI patients with other study

Studies	Percentage
Paul J Dasgupta and Others[34]	84%
Present study	90%

In the present study 90% of AKI patients have WBCT >20 minutes which is consistent with paul j dasgupta in which it was 84% of AKI patients.

7.Significant variables

Table 25: Comparison variables with significant p-value for the development of snake bite induced AKI with other study

Variables	Athappan G and Others[29]		Present study	
	Percentage	p-value	Percentage	p-value
Signs of inflammation	98.7%	Not significant	86.2%	1.00
Lapse of time >12 hours	55%	0.0003	30%	0.005
Mean Cr in mg/dl	4.24	0.01	2.6	<0.001
Mean B. urea in mg/dl	100.65	0.01	73.5	<0.001

Clinical variables like signs of inflammation, lapse of time of >12 hours in presenting to the hospital, mean serum creatinine and mean blood urea elevations with significant p-value is comparable with Athappan G and others study.[29]

CONCLUSION

From our study we conclude that

1. Common manifestations of poisonous snake bite include cellulitis, abnormal coagulation profile and decreased urine output.
2. Majority of the patients with AKI presented with reduced urine output.
3. Incidence of AKI was seen in 30.7% of snake bite patients.
4. Overall mortality due to snake bite induced AKI is 4.6 %.
5. Lapse of time in presenting to the hospital and abnormal coagulation profile are the predictors of poor outcome in snake bite induced acute kidney injury.

SUMMARY

This study is a descriptive study of 65 randomly selected patients with snake bite induced AKI. These patients were admitted to Shri B.M Patil Medical College,Hospital and Research Center, from August 2018 to August 2020.

In our study, mean age of patients studied was 36.9 years. Male to female ratio was 1.7:1 with male preponderance. The mean interval between snakebite and presentation to BLDE Hospital was 15.37 hours. All snake bites were inflicted to lower limbs and 51 % of snake bites were due to Viper as identified by patients.

Out of 65 patients, AKI was seen 20 patients (31%) of which 10 patients had thrombocytopenia (50%). 86% of patients presented with local signs of inflammation indicating the vasculotoxic nature of envenomation. 75% of patients presented with coagulation abnormality.

28 patients (43%) were having decreased urine output ,of which 75% (15 patients) were associated with AKI. Out of 37 patients (57%) of normal urine output 25%(5 patients) had AKI . Need for haemodialysis was seen in 6 patients of which 3 patients survived .

Out of 17 patients who presented after twelve hours of snake bite 11 patients (64.7%) had AKI.

Out of 20 patients with AKI 9 patients (45%) are in AKI stage I, 7 patients (35%) are in AKI stage II,4 patients (20%) are in AKI stage III on admission. After three day of follow up majority of patients in stage I and stage II were improved and patients in stage III renal failure underwent hemodialysis.

LIMITATIONS OF THE STUDY

1. Sample size was small, i.e. only 65.
2. Identification of snake was not possible in all cases.
3. Follow up for chronic kidney disease was not possible.

NORMAL REFERENCE VALUES OF VARIOUS PARAMETERS OF THE STUDY

S.No	**Parameter**	**Normal Range**	**Source**
1.	**Serum Creatinine**	**0.7 to 1.4 mg/dl**	**vasudevan text book of Biochemistry 8th edition pg no.693**
2.	**Blood Urea**	**20 to 43 mg/dl**	**vasudevan text book of Biochemistry 8th edition pg no.694**
3.	**Platelet count**	**1.5 to 4 lakhs**	**A Manual of laboratory and diagnostics tests by Frances Fishback, 9th edition, pg.no 64**
4.	**APTT**	**21-37 sec**	**A Manual of laboratory and diagnostics tests by Frances Fishback, 9th edition, pg.no 156**
5.	**INR**	**1-1.5**	**A Manual of laboratory and diagnostics tests by Frances Fishback, 9th edition, pg.no 159**

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ANNEXURE I

ETHICAL CLEARENCE CERTIFICATE

B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103 IEC.NO-280/18
17/11/2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 PM scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title : Study of acute kidney injury in snake bite patients.

Name of P.G. Student : Dr Ravi Teja
Department of General Medicine.

Name of Guide/Co-investigator: Dr.Siddanagouda.M.Biradar,Associate Professor of General Medicine.

DR RAGHAVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization:

1) Copy of Synopsis/Research Project
2) Copy of informed consent form.
3) Any other relevant documents.

ANNEXURE II

INFORMED CONSENT FORM:

TITLE OF RESEARCH: **STUDY OF ACUTE KIDNEY INJURY IN SNAKE BITE PATIENTS**

GUIDE : **DR SIDDANGOUDA M BIRADAR**

MD MEDICINE

P.G. STUDENT : **DR RAVI TEJA**

All aspects of this consent form are explained to the patient in the language understood by him or her.

PURPOSE OF STUDY:

I have been informed that the purpose of this study is to study the incidence and in hospital out come of Acute Kidney Injury in snake bite patients.

PROCEDURE:

I understand that I will undergo detailed history and clinical examination and investigations

BENEFITS:

I understand that my participation in this study will have no direct benefit to me other than the potential benefit of treatment which is planned to prevent further morbidity and mortality in me.

CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulation of hospital. If the data is used for publication the identity will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw from study at any time.

(Signature of Guardian)

(Signature of patient)

STUDY SUBJECT CONSENT FORM:

I confirm that **Dr. RAVI TEJA** has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all above in detail in my own language and I understand the same. I agree to give my consent to participate as a subject in this research project.

DATE SIGNATURE OF PARTICIPANT

DATE SIGNATURE OF WITNESS

ANNEXURE III

PROFORMA

Name :

IP No. :

Age /sex: date of admission :

Occupation :

Address :

A. Presenting complaints

B. History of presenting complaint

Lapse of time after the snake bite:

Type of alternative treatment before coming to hospital: Tourniquet application:

Identification of the snake: Urine output:

Hematuria:

Bleeding from the gums: Drooping of eyelids

[PTOSIS]: Loss of consciousness:

Convulsions:

Difficulty in breathing: Headache:

Vomiting:

Bite site:

Fang marks:

Local swelling:

Associated with pain:

Bleeding from the bite site:

C. Past history

Hypertension: Yes/No

Diabetes mellitus: Yes/No

Pre-existing renal disease: Yes/No

D. Personal history

Appetite: normal/decreased

Diet: veg/mixed

Sleep: disturbed/normal

Bladder: normal/Decreased: Yes/No

Bowel habits:

Additional habits:

smoking Alcohol consumption

E.Menstrual history

Cycle: duration:

Flow: scanty/moderate/heavy

F.General physical examination

built:well/moderate/poorly nourishment:

vitals: blood pressure: mmHg in right upper limb in supine position pulse rate: bpm

regular/irregular volume:

character:

vessel wall:

All the peripheral pulses equally felt/not felt

Radioradial/radiofemoral delay: Yes/No

Respiratory rate: cycles/min

Temperature:

Pallor: present/not present Icterus:

Yes/No Clubbing: Yes/No

Cyanosis: Yes/No

Lymphadenopathy: yes/No

Bleeding from gums: Yes/No

Local examination of the bite site:

skin:

fang mark:

bleeding from the site:

local edema:

temperature: raised/ not raised

tenderness: present/not present

peripheral pulses: felt/not

G.Systemic examination

Cardiovascular system:

Respiratory system:

Per abdomen:

CNS examination:

H.Investigations

1. Complete hemogram:
2. Whole blood clotting time:
3. Bleeding time:
4. Blood urea:

   baseline:

   at 24 hours:

   2nd day:

   3rd day:
5. Serum creatinine:

   baseline:

   at 24 hours:

   2nd day:

   3rd day:
6. Creatine kinase:
7. Prothrombin time:
8. Partial thromboplastin time:
9. USG abdomen

10. Urine output:

    baseline:

    at 24 hours:

    2nd day:

    3rd day:

11. Diagnosis

12. Treatment given

13. Hemodialysis:

14. Need for hemodialysis: Yes/No

    number of cycles underwent: after 1st cycle 2nd 3rd 4th 5th 6th 7th 8th

    Blood. urea:

    S. creatinine:

    Urine output:

I. Conclusion and comment

Master chart key:

" + " - Present

" - " – Absent

" N " – Normal

" NP " – Not Palpable

" NR " – Not Recordable

" ↑ " – Increased

" MRD " – Medical Renal Disease

" Y " – Yes

" INR " – International Normalised Ratio

" WBCT "- whole blood clotting time

" aPTT "-Activated Partial thromboplastin Time

Master Chart

s.no.	Name	ip no.	Age	sex	site of bite	lapse of time in hrs	alternative treatment	tornique application	identification of snake	reduced urine output	hematuria	bleeding from gums	vomiting	pulse	BP		fang marks	signs of inflamation	bleeding from bite site	peripheral pulse	hb in gms	total count	platelet count (lakhs)	wbct in minutes	bleeding time
															systole	diastole									
1	chaitra narayan	14435	38	F	Rt leg	2	-	+	No	+	-		-	86	130	80	+	+	-	+	11.0	5800	2.8	<20	N
2	parvathi hiremath	16837	55	F	Rt leg	½	-	+	No	+	-	-	-	120	90	70	+	+	-	+	8.9	21,410	1.82	>20	↑
3	malakappa	15766	17	M	Lt foot	6	-	+	Viper	N	-	-	-	88	110	80	+	+	+	+	11.8	7,600	1.71	>20	↑
4	mallappa gurappa	15742	45	M	Lt foot	4	-	+	Viper	+	-	+	-	84	110	80	+	+	+	+	2.5	3,600	1.2	>20	↑
5	sonnawwa	15843	50	F	Rt foot	12	+	+	No	+	-	-	-	94	120	80	+	+	-	+	10.5	9,100	0.51	>20	N
6	siddawwa	15983	40	F	Lt leg	9	+	+	No	+	-	-	-	86	130	80	+	+	-	+	14.0	6,400	2.8	>20	N
7	shrishail basalingappa	15804	60	M	Rt leg	29	-	-	Viper	+	-	-	-	66	94	60	+	+	-	+	5.0	21,700	0.27	<20	N
8	kasturi sharanappa	15635	45	F	Rt foot	2	-	+	No	+	-	-	2	72	110	70	+	+	-	+	11.0	6,400	2.5	>20	N
9	renuka kanteppa	15451	30	F	Lt leg	19	-	+	No	+	-	+	2	NP	NR	NR	+	+	+	NP	7.2	4,000	2.1	<20	N
10	siddappa basalingappa	15997	62	M	Lt leg	48	-	+	No	+	-	-	-	86	140	80	+	+	-	+	10.7	8,800	0.93	<20	N
11	kavita roopesh	12895	22	F	Lt leg	4	-	+	Viper	+	-	+	-	82	114	70	+	+	+	+	10.4	4,800	2.4	>20	↑
12	shankarappa yallapa	14939	52	M	Lt leg	6	-	+	No	+	-	-	-	80	124	72	+	+	-	+	10.1	7,400	1.9	>20	N
13	basavaraj	15656	35	M	Lt 2 toe	1	-	+	No	N	-	-	-	88	110	80	+	+	-	+	9.3	6,800	2.8	>20	N
14	ramachandra rathod	10750	55	M	Lt leg	7	-	+	No	+	-	-	-	84	120	90	+	+	-	+	8.9	8,900	2.25	>20	N
15	vijay sangangouda	11187	30	M	Lt 1 toe	4	-	+	No	+	-	+	-	88	110	80	+	+	+	+	11.4	5800	1.63	>20	N
16	shobha biradar	12628	21	F	Rt 3 toe	2	-	+	No	N	-	-	-	80	118	80	+	+	+	+	11.7	31,100	1.25	>20	N
17	mahantesh	11386	23	M	Lt calf	4	-	+	No	N	-	-	-	80	90	70	+	+	+	+	10.2	4,200	2.8	<20	N
18	mahadev	12214	50	M	Lt foot	24	-	+	No	+	-	-	-	90	80	50	+	+	-	+	10.0	11,000	1.7	>20	N
19	savithri parashuram	12491	20	F	Lt shin	24	+	+	Viper	+	-	-	4	88	130	80	+	+	-	+	8.8	13,440	0.53	>20	N
20	balaram	12662	33	M	Lt foot	4	-	+	No	N	-	-	1	90	110	60	+	+	-	+	10.8	5,900	0.57	>20	N
21	sidu ganapathi	9061	35	M	Rt foot	3	-	-	No	+	-	-	3	90	110	80	+	+	-	+	10.1	6,400	1.9	>20	N
22	prashant aravind	8705	28	M	Lt foot	>96	+	+	Viper	+	-	-	4	90	100	80	+	+	-	+	8.0	18,00	1.7	<20	N
23	bagamma mallappa	9536	34	F	Lt 2 toe	48	-	+	No	N	-	-	-	66	120	80	+	+	-	+	9.0	6,300	2.8	<20	N
24	dundappa saibanna	18040	45	M	Rt leg	16	-	+	Viper	+	-	-	-	100	90	50	+	+	-	+	9.8	17,600	0.3	>20	N
25	savithri	8284	23	F	Rt foot	4	-	-	No	N	-	-	10	92	120	80	+	+	-	+	9.0	5,100	2.1	>20	N
26	bouramma	860	26	F	Rt foot	4	-	+	No	N	-	-	-	76	120	70	+	+	-	+	10.8	8,400	3.1	<20	N
27	menakshi shantappa	3944	26	F	Lt foot	6	-	-	Viper	+	-	-	2	89	118	80	+	+	-	+	10.2	6,400	2.1	>20	N
28	asha	4872	16	F	Rt leg	24	-	-	Viper	N	+	+	3	100	100	60	+	+	+	+	4.3	11,400	0.75	<20	↑
29	neelabai	5390	40	F	Rt foot	3	-	-	No	N	-	-	-	84	100	80	+	+	-	+	11.0	6,000	2.7	>20	N
30	laxman saibanna	26870	55	M	Lt shin	10	-	-	Viper	+	-	+	2	102	90	60	+	+	+	+	6.0	4,600	2	>20	N
31	shivanand	27823	32	M	Lt foot	96	+	-	Viper	+	-	-	-	110	94	60	+	+	-	+	10.4	8,600	1.8	<20	N
32	ramesh mallappa	28167	44	M	Lt foot	4	-	-	Viper	+	+	+	-	92	100	70	+	+	+	+	6.0	10,400	1	>20	↑
33	sunita	28170	17	F	Lt leg	5	-	-	Cobra	+	-	-	-	104	100	60	+	+	-	+	10.8	4,800	3.1	>20	N
34	hajibaba	27292	16	M	Lt calf	4	-	+	No	N	-	-	-	110	94	60	+	+	-	+	9.8	7,400	1.9	>20	N
35	takkappa basappa	26337	35	M	Rt leg	4	-	-	No	+	-	-	4	100	100	60	+	+	+	+	9.0	5,100	2.1	<20	N
36	gadyappa bhimanna	26991	66	M	Lt leg	48	-	+	Viper	+	+	-	-	88	110	80	+	+	+	+	10.0	8,000	1.1	>20	N
37	chandan	27014	23	M	Lt leg	4	-	+	Viper	+	+	+	-	82	114	70	+	+	+	+	10.2	5,800	0.5	>20	↑
38	suresh	26712	24	M	Lt leg	14	-	-	Viper	+	+	-	4	NP	NR	NR	+	+	+	NP	9.7	4,000	2	<20	N
39	sanju sadawa	25388	30	M	Lt leg	6	-	-	No	N	-	-	3	92	100	74	-	+	-	+	10.2	4,600	2.7	>20	N
40	ashabi	23517	65	F	Lt foot	1	-	-	Viper	N	-	-	-	88	116	70	+	+	-	+	9.3	10,400	3.1	>20	N
41	gunabi ekanath	22598	28	F	Lt leg	7	-	+	Viper	N	-	-	-	84	120	90	+	+	-	+	8.9	8,900	2.3	>20	N
42	prabhuray	22445	51	M	Lt leg	8	+	+	Viper	+	+	+	2	84	130	80	+	+	-	+	7.4	5,800	1.6	>20	↑
43	basappa shivappa	14762	30	M	Rt foot	24	+	+	Viper	+	-	-	5	100	80	50	-	+	-	+	9.8	6,400	2.7	<20	N
44	saibanna	18879	29	M	Rt foot	3	-	-	Viper	N	-	-	-	80	100	70	+	+	-	+	11.7	11,100	1.25	>20	N
45	rajashree	33117	35	F	Lt calf	4	-	-	Viper	N	-	-	2	90	90	70	+	+	+	+	7.2	4,200	2.2	>20	N
46	manigen ramappa jalli	14271	55	M	Rt calf	6	-	+	No	N	-	-	-	76	130	80	+	+	+	+	12.2	6,800	3.2	>20	N
47	chetan suryakanth	11760	28	M	Lt foot	3	-	+	No	N	-	-	-	100	124	74	+	+	-	+	9.0	6,300	2.7	>20	N
48	banudas namdev	10014	32	M	Rt 2 toe	2	-	-	Viper	N	-	-	2	100	90	70	+	+	-	+	10.2	4,200	2.7	<20	N
49	ambarish gouda	10740	36	M	Lt leg	>96	+	-	Viper	+	+	-	10	92	90	60	+	+	-	+	6.8	4,600	3.2	<20	N
50	sagar	16885	16	M	Rt foot	4	-	-	No	N	-	-	10	92	104	64	-	-	-	+	9.0	5,100	2.6	>20	N
51	kashibai	12954	35	F	left calf	3	-	+	Cobra	N	-	-	2	92	110	70	-	-	-	+	10	8,200	3	<20	N
52	mehaboob kutbuddin	20456	17	M	Rt foot	4	-	-	No	N	-	-	-	90	116	70	+	-	-	+	11	8000	2.8	<20	N
53	lakshman arjun	20465	20	M	Lt foot	6	-	-	No	N	-	-	-	86	126	80	-	-	-	+	12	8200	2.3	<20	N
54	mahadev	18642	40	M	Rt calf	3	-	-	Cobra	N	-	-	-	94	140	80	+	+	-	+	11	9000	1.8	<20	N
55	chinnaswamy	14828	46	M	Lt foot	4	-	-	No	N	-	-	-	90	146	86	+	-	-	+	10	7000	1.9	<20	N
56	siddaraju	15602	38	M	Lt calf	4	-	-	krait	N	-	-	-	86	136	80	+	+	-	+	12	6200	2.4	<20	N
57	sakkama	12802	40	F	Rt foot	5	-	-	No	N	-	-	-	92	140	90	+	-	-	+	11	7200	2.2	<20	N
58	revanna	18290	44	M	Rt calf	4	-	-	No	N	-	-	-	90	140	86	+	-	-	+	13	8500	2	<20	N
59	nandisha	15526	40	M	Lt foot	3	-		no	N	-	-	-	98	110	70	+	+	-	+	11	7600	1.7	<20	N
60	ratnamma	14202	48	F	Rt calf	3	-	+	cobra	N	-	-	-	96	116	80	+	+	-	-	12	7800	1.9	<20	N
61	subbamma	14612	52	F	Lt foot	4	-	-	no	N	-	-	-	94	110	70	+	+	-	+	13	8200	1.8	<20	N
62	manglamma	16826	54	F	Rt hand	3	-	-	cobra	N	-	-	-	92	150	90	+	+	-	-	12	8600	2	<20	N
63	mahalinga	10278	48	M	Rt calf	5	-	-	no	N	-	-	-	90	140	90	-	-	-	+	13	9000	2.1	<20	N
64	venugopal	10548	46	M	Rt foot	4	-	+	krait	N	-	-	-	92	140	86	+	+	-	+	14	10000	1.8	<20	N
65	jayanthi	10426	32	F	Lt foot	4	-	-	no	N	-	-	-	98	146	90	-	-	-	+	15	11000	1.8	<20	N

Master Chart

blood urea				Sr. Creatinine				Creatine kinase	PT-INR	APTT	USG Abdomen	Urine output in ml				eGFR	ASV vials given	Supportive tretment					Need for hemodialysis	no. of cycles	After 1st cycle			At the end			End Result
base line	at 24 hrs	2nd day	3rd day	base line	at 24 hrs	2nd day	3rd day					base line	at 24 hrs	2nd day	3rd day			IVF	Antibiotics	FFP	Platalets	Whole blood			Blood urea	Serum creatinine	Urine output	Blood urea	Serum creatinine	Urine output	
41	67	67	36	1.7	1.2	1.8	1	200	1.0	40	N	950	1500	1700	2700	110	12	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
39	34	52	88	0.3	0.9	1.7	1.3	180	1.3	43	N	800	800	1200	1600	108	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
20.9	31	28	-	0.9	1.4	0.8	-	345	1.0	12	N	1000	1500	2000	2000	106	20	+	+	2	-	-	-	-	-	-	-	-	-	-	IMPROVED
31	118	98	60	1.2	2.9	1.8	1.4	320	1.0	4	N	200	900	2000	2500	116	25	+	+	-	-	3	-	-	-	-	-	-	-	-	IMPROVED
98	121	142	100	4.4	5.3	7.8	5.2	400	1.0	44	N	600	800	1000	1000	12	30	+	+	-	-	-	-	-	-	-	-	-	-	-	CKD
58	55	121	74	1.2	2.0	3.1	2.5	250	1.0	45	N	800	1000	1000	2000	112	48	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
74	110	121	89	4.6	6.0	6.5	6.2	498	1.7	40	MRD	Nil	Nil	60	100	30	40	+	+	-	-	-	+	6	121	6.5	Nil	55	2.8	1000	IMPROVED
34	52	48	45	0.9	1.4	1.8	1.3	160	1.0	30	N	800	1000	1500	2000	96	25	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
92	125	89	65	1.2	1.7	1	1.1	320	1.6	30	N	15	1200	2200	2500	98	30	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
43	86	67	39	2.0	2.4	1.6	1.3	128	1.2	48	N	1000	1500	2000	2000	46	-	+	+	-	4	-	-	-	-	-	-	-	-	-	IMPROVED
34	72	50	53	1.2	1.5	0.8	0.7	200	0.9	22	N	800	1000	1500	2000	98	30	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
47	29	32	-	0.7	1.1	1.4	1.2	240	1	26	N	800	800	1000	1500	110	19	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
23	40	52	48	0.7	1.4	1.3	1.2	180	1	20	N	2000	2500	2500	2500	102	11	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
15	48	99	96	1.1	1.6	2.5	2.1	188	1	28	MRD	600	1000	1500	2000	110	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
70	72	68	62	1.5	2.1	1.4	1	128	3.1	120	N	800	1000	1250	2000	106	30	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
35	65	22	28	1.3	1.6	1	0.8	200	1	22	N	4000	3500	3000	3500	108	5	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
50	79	26	17	0.8	1.2	0.6	0.6	178	1	28	N	2000	2500	2500	2000	100	-	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
192	188	119	106	6.9	9.5	6.7	5.4	498		44	MRD	100	100	500	800	30	20	+	+	-	-	-	y	6	-	-	-	-	-	-	CKD
22	105	98	96	1.6	4.8	4.2	2.1	168	1	32	N	500	1000	1500	2000	98	15	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
22	63	29	29	1.1	1.6	0.9	0.9	164	1	29	N	1500	2000	2000	2000	96	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
48	52	84	60	0.8	1.4	1.8	1.5	188	1	40	N	750	1000	1500	2000	108	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
198	176	135	78	20.0	21.0	14	12	560	1.5	40	MRD	100	100	500	500	18	-	+	+	-	-	2	+	4	135	14	500	-	-	-	DEATH
28	35	33	29	0.5	0.9	0.8	0.6	118	1	29	N	3000	2800	3000	3000	117	-	+	-	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
88	88	105	142	3.4	5.0	4.5	3.8	450	1.5	34	MRD	400	800	1200	2000	106	25	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
98	102	92	25	2.0	2.8	2.6	1.2	178	1	29	MRD	2500	2800	3000	3000	108	15	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
34	52	48	41	0.9	1.4	1.3	1	110	1	30	N	2500	2000	3000	2500	112	-	+	-	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
45	68	52	48	1.8	2.3	2.1	1.9	168	1	29	N	600	1000	1500	1500	110	25	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
65	108	140	152	4.2	5.8	7.2	7	333	1.5	44	MRD	50	50	100	150	12	20	+	+	-	-	2	+	3	140	7.2	100	-	-	-	DEATH
48	52	45	34	1.4	1.8	1.3	0.9	172	1	29	N	3000	2500	2500	2500	96	10	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
89	115	72	65	1.2	1.7	1.1	1.2	310	1	29	N	100	800	2000	2500	98	10	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
135	162	176	155	12.4	14.2	21	18	424	1	32	MRD	100	150	150	100	15	-	+	+	-	-	-	+	1	155	18.0	150	-	-	-	DEATH
35	48	55	48	0.9	1.4	1.5	1.3	289	3	50	MRD	500	500	600	1000	90	20	+	+	4	-	2	-	-	-	-	-	-	-	-	IMPROVED
36	48	33	18	1	1.5	1.3	1.1	164	1	30	N	900	900	1000	1500	96	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
50	80	32	26	0.8	1.2	0.6	0.6	192	1	29	N	2000	2000	2500	3000	118	10	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
92	102	25	28	2.5	2.8	1.2	1.2	132	1	32	MRD	500	600	1000	1500	102	-	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
67	86	39	28	1.5	2.2	1.3	1.4	258	1.2	48	MRD	800	1000	2000	2500	110	-	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
34	72	50	53	1.2	1.6	0.8	0.7	228	1.1	38	N	1000	1500	2500	2500	112	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
92	125	89	65	1.3	1.7	1.5	1	320	1.6	32	MRD	50	500	1200	2200	116	30	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
35	47	29	29	1	1.4	1.2	1.2	162	1	29	N	1000	1500	2000	2200	120	15	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
23	40	45	38	0.7	1.2	1.4	1	218	1	31	N	2000	2500	2000	2500	122	11	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
25	48	99	96	1.1	1.6	2.5	2.2	340	1.5	40	MRD	2000	2000	2500	2500	124	25	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
70	72	80	78	1.5	2.1	2.3	1.9	218	3.1	90	MRD	800	1000	1250	2000	116	30	+	+	4	-	-	-	-	-	-	-	-	-	-	IMPROVED
119	192	188	160	6.7	6.9	9.5	8.2	336	1.3	32	MRD	100	100	100	100	9	-	+	+	-	-	-	+	8	188	9.5	100	132	5.9	800	CKD
22	35	68	42	1	1.2	1.6	1.4	198	1.2	29	N	3000	3500	3000	3000	120	10	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
50	79	36	17	0.8	1.3	0.6	0.6	298	1	32	N	2000	2500	3000	3000	116	10	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
68	72	90	84	1.1	1.2	1.6	2.1	360	1	34	N	2500	2500	3000	3000	120	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
40	52	68	62	0.7	1.1	1.4	1.3	362	1	36	N	2500	3000	3000	2500	104	10	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
79	84	62	56	1.2	1.6	1.3	0.8	340	1	36	N	2500	2500	3000	3000	126	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
105	142	180	196	4.8	6.2	6.8	7.2	668	1.5	40	MRD	50	50	100	100	12	-	+	+	-	-	-	+	7	180	6.8	100	140	5.8	1000	CKD
92	102	35	28	2.4	2.9	2.6	1.9	290	1.2	34	MRD	2500	2500	3000.0	2500	120	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
46	44	42	44	0.9	1	1.1	0.9	112	1.6	32	MRD	2200	2100	2150	2300	102	10	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
42	40	44	44	0.8	0.9	0.8	1	106	1.8	35	N	2000	1900	1950	2050	102	15	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
46	44	44	46	1	0.9	1.1	1.1	110	2	32	N	1800	1900	1850	1950	120	10	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
46	44	40	42	1.2	1	1.1	1.1	112	1.8	34	N	1850	1900	1950	2000	126	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
44	46	48	45	1.1	1.1	1.1	1.2	120	2	32	N	1800	1800	1850	1800	118	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
46	48	50	46	1	1.1	1	0.9	108	1.8	34	N	1850	1900	1900	1950	120	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
48	46	46	46	1.1	1.2	1.1	1.2	112	2	32	N	1700	1750	1800	1850	126	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
44	42	48	48	1.1	1.1	1	1.1	110	2.2	36	N	1750	1800	1850	1900	118	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
50	52	48	50	1.2	1.3	1.1	1.2	116	1.8	34	N	1800	1850	1750	1800	120	25	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
48	50	48	50	1.3	1.2	1.2	1.1	110	1.8	36	N	1800	1750	1850	1800	116	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
52	50	50	52	1.2	1.1	1.2	1.2	106	1.6	34	N	1700	1750	1750	1800	118	25	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
46	42	44	46	1.2	0.9	1	1	104	1.4	35	N	1650	1700	1800	1850	120	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
44	44	45	46	1.1	1	1.1	1.2	106	1.6	34	N	1700	1750	1700	1800	124	25	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
42	42	44	44	1.1	1.2	1.1	1	108	1.8	32	N	1750	1800	1750	1750	116	30	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED
48	48	46	46	1.4	1.2	1.2	1.3	110	2	32	N	1650	1700	1750	1800	118	20	+	+	-	-	-	-	-	-	-	-	-	-	-	IMPROVED