VOLUME - 14, ISSUE - 03, MARCH - 2025 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

General Medicine

SNAKEBITE-MEDIATED ACUTE KIDNEY INJURY:

Dr. Manam Chinmayi Chowdary — House surgeon KIMS And RF Amalapuram, Andhrapradesh Konaseema Institute Of Medical Sciences And Research

Dr. Pradeep Garapati — House surgeon KIMS And RF Amalapuram, Andhrapradesh Konaseema Institute Of Medical Sciences And Research

ABSTRACT Snakebite envenomation is a significant global health concern, particularly in tropical and subtropical regions. Acute kidney injury (AKI) is a common and serious complication, leading to increased morbidity and mortality. The pathophysiology of snakebite-mediated AKI involves direct nephrotoxicity, hemotoxicity, rhabdomyolysis, and immune-mediated mechanisms. Early diagnosis and prompt management are crucial to improving outcomes. This review explores the mechanisms, clinical presentation, diagnostic approach, and therapeutic strategies for AKI following snakebite envenomation.

KEYWORDS :

INTRODUCTION

Snakebite is a neglected tropical disease and major medical problem that affects millions worldwide, particularly in rural areas of South Asia, sub- Saharan Africa, and Latin America. Viper bite is most important cause of snake bite mortality and morbidity in this region . The annual mortality is around 30000 most of them from south east asia and west africa. Approximately 10000 deaths occur in India. However the factors influencing mortality in these area have not been fully defined. Among the systemic complications of snake envenomation, AKI is one of the most serious, with potential progression to chronic kidney disease (CKD) or death if not managed appropriately. Understanding the pathophysiology, clinical features, and treatment strategies for snakebite-induced AKI is crucial for improving patient outcomes

Pathophysiology

Approximately hundred different kinds of peptides or proteins, lipids, amines, carbohydrates etc,have been isolated from snake venoms,though not all of which are toxic to humans.[1] Digestive hydrolases, hyaluronidase, and polypeptide cytotoxins contribute to the local tissue necrosis seen after bites of some snakes.[2] Enzymatic toxins in snake venom result in injuries to all kidney cell types including glomerular, tubulo-interstitial and kidney vasculature.

Hemorrhagins causes spontaneous bleeding by directly injuring the vascular endothelium. Activaton or inhibition of various coagulation proteins or platelets, and endothelial disruption caused by phospholipases, serine proteases, metalloproteinases, disintegrins and C-rype lectins lead to coagulopathy.[3] Myotoxic phospholipase A2 seen in venoms of some vipers and sea snakes is responsible for rhabdomyolysis which can later lead to acute renal failure. The Secondary effects of necrosis and ischemia together with inflammatory response mounted by host in response to environment potentiate the cascade of events leading to further deterioration. Hypotension without any bleeding manifestation can be caused by permeability factor that increases extravastation and direct and indirect effect on cardiac muscle and vascular smooth muscle . [1] Oligopeptides potentiates bradykinin action, sarafotoxins have homology to endothelin, vascular endothelial growth factor and natriuretic peptides.[4 5 6] Neurotoxins acts on neuromuscular junction pre synaptically or post synaptically. Haemodynamic response to snake bite specifically haematotoxic viper bite is similar to sepsis , and altered haemodynamics are probably central to pathogenesis of renal failure.[7] Hemorrhage leading to intravascular volume depletion, hemolysis, rhabdomyolysis and disseminated intravascular coagulation are other factors involved in pathogenesis. Hemotoxic and myotoxic actions of snake venom have good correlation with nephrotoxicity[8] The occasional occurrence of renal failure in a patient without these factors may have direct nephrotoxic effect. Both structural and functional changes in cells of glomerulus, proximal tubules, distal tubules and vascular endothelium have been seen in experimental models of SAKI[6] Immune complex glomerulonephritis have a very minor role. The significance of glomerular lesions observed in patients with snake bite is uncertain.[5]Primary glomerular involvement is uncommon in snake bite envenomation.

The experimental data in this regard suggests that mesangiolysis is an early and most consistent abnormality associated with snake bite envenomation.[5] Mild focal and segmental mesangial proliferation is the most common. [7] Severe form of glomerular involvement may include crescentic glomerulonephritis or diffuse proliferative glomerulonephritis these are very rare.[9] If recovery of patient is very slow and renal failure persists for more than 4 wk probable cause is cortical necrosis or tubulointerstitial nephritis with acute tubular necrosis or crescentic glomerulonephritis.[9] Severe tubular and vascular lesions, increased rates of apoptosis in distal tubular epithelial cell,and presence of eosinophills, mast cella and hyperplastic fibroblasts in the interstitium are some of the features of snake bite induced acute tubular necrosis . For some unknown reasons the incidence of acute cortical necrosis is more in india as compared to other south asian countries . [10] morphological pattern of i jury in snake bite

- Acute renal failure
- Acute tubular necrosis
- Acute diffuse interstitial nephritis
- Acute cortical necrosis
- Vasculitis
- Extracapillary proliferative (cresentic) glomerulonephritis

[11]Acute cortical necrosis, patchy or diffuse, is the most dreaded histopathological finding as it confers very poor renal survival .[2] Pathogenesis of kidney injury due to snake envenomation Includes ischaemia secondary to decreased kidney blood flow caused by systemic bleeding and vascular leakage, proteolytic degradation of the glomerular basement membrane by snake venom metalloproteinases (SVMPs), deposition of microthrombi in the kidney microvasculature (thrombotic microangiopathy), direct cytotoxic action of venom, systemic myotoxicity (rhabdomyolysis) and accumulation of large amounts of myoglobin in kidney

tubules.

[12 13 14 15] **Factors That Contibute To AKI**

- **Venom toxicity**: Direct nephrotoxicity from the venom
- **Coagulopathy**: Bleeding disorders, including prolonged bleeding time and prothrombin time
- **Hypotension**: Low blood pressure
- **Circulatory Collapse**: Blood circulation problems
- **Intravascular Hemolysis**: Red blood cell breakdown
- **Disseminated Intravascular Coagulation**: Blood clotting issues
- **Rhabdomyolysis**: Muscle damage
- **Complement Activation**: Part of the immune system's response
- **Secondary Sepsis**: Infections that can occur after snake bites

Clinical Manifestation

Snake Venom

[16 17] Snake venom may contain twenty or more toxins. Most of them are enzymes, non-enzyme peptide toxins and non-toxic proteins. The cobra and krait venoms are neurotoxic and cardiotoxic. Local effects are seen in the former but not in the latter. Viper venom is vasculotoxic and has severe necrotizing local effects. The neurotoxins of elapids and sea snakes are absorbed rapidly into the blood stream (therefore causing rapid systemic effects), whereas the much larger molecules of viper venom are taken up more slowly through the lymphatics (therefore causing severe local effects). Most venoms do not cross blood brain barrier

Clinical Features

Dry Bites

[16]In at least 20% of pit viper bites and a greater percentage of elapid and sea snake bites, no venom is injected

Local Features

Fang Marks: Generally, the presence of two puncture wounds indicates a bite by a poisonous snake. In the case of a non-venomous snakebite, small puncture wounds are seen arranged in an arc.

Pain: Burning, bursting or throbbing pain may develop immediately after the bite and spread proximally up the bitten limb. Draining lymph nodes soon become painful. Krait and sea snake bites maybe virtually painless.

[18]**Local swelling :** Viper bites produce more intense local reaction than other snakes. Swelling may become apparent within 15 minutes and becomes massive in 2-3 days. It may persist for up to 3 weeks. The swelling spreads rapidly from the site of the bite and may involve the whole limb and adjacent trunk. Regional lymphadenopathy may develop. In case the envenomed tissue is contained in a tight fascial compartment like the pulp space of digits or anterior tibial compartment, ischaemia will develop. If there is no swelling 2 hours after a viper bite, it is safe to assume that there has been no envenoming

Local Necrosis: In viper bites, bruising, blistering and necrosis may appear over few days following the bite. Necrosis is marked following bites of Asian pit vipers, and some rattlesnakes. Bites by Asian cobras can also cause tender local swelling and blistering. Krait bites usually do not cause any local reaction. Patients spat at by spitting elapids may develop venom ophthalmia.

Secondary Infection: Bacterial flora in the oral cavity of the snakes contributes to secondary infection.

General Features :-

[18]Even in patients with 'dry bites', symptoms like flushing, breathlessness, palpitations, and dizziness, tightness in the chest, sweating and acroparaesthesiae are common. These are due to anxiety and sympathetic overactivity. Apart from these, early symptoms in elapid bites include vomiting, heaviness of eyelids, blurring of vision, hypersalivation, congested conjunctivae and 'gooseflesh'. In krait bites, cramping abdominal pain followed by diarrhoea and collapse may occur. Sea snake envenomation causes headache, a thick feeling of the tongue, thirst, sweating and vomiting. It is important to remember that nausea and vomiting are common symptoms of all severe envenomation

Systemic Features:-

[17]Clotting defects and haemolysis: Haemostatic abnormalities are characteristic of envenoming by Viperidae. Persistent bleeding from fang puncture wounds, venepuncture or injection sites, and other new and partially healed wounds suggest that the blood is incoagulable. Spontaneous systemic haemorrhage is most often detected in the gingival sulci. Epistaxis, haematemesis, cutaneous ecchymoses, haemoptysis, subconjunctival, retroperitoneal and intracranial haemorrhages are also reported. Viper and sea snake venoms also cause intravascular haemolysis .

Neurotoxicity: Elapid and sea snake venoms have significant [18]neurotoxicity. Following an elapid bite, paralysis is first detectable as ptosis and external ophthalmoplegia appearing as early as 15 minutes after the bite. Sometimes the onset maybe delayed for 10 hours or more. Later the face, palate, jaws, tongue, vocal cords, neck muscles, and muscles of deglutition become paralysed. Airway obstruction or paralysis of the intercostal muscles and diaphragm cause respiratory failure. Neurotoxic effects are completely reversible either acutely in response to antivenom or anticholinesterases or may wear off spontaneously in 1 to 7 days. It is important to note that these neurotoxins do not cross blood brain barrier and do not alter consciousness.

Myotoxicity: Sea snake venom contains myotoxins that cause myalgias, myopathy and rhabdomyolysis. Generalized aching, stiffness and tenderness of muscles develop 0.5 to 3.5 hours after the bite. Trismus is common. Myoglobinuria secondary to rhabdomyolysis appears 3 to 8 hours after the bite.

Cardiotoxicity: Viper and elapid venom can cause direct myocardial damage manifesting as arrhythmias, bradycardia, tachycardia or hypotension

Nephrotoxicity: Renal failure is secondary to ischaemia in Viper bites (especially Russell's viper).

Shock: A variety of factors contribute to shock. They include fright, hypovolemia (due to extravasation of fluids and blood loss), myocardial depression, haemorrhage into the adrenals and pituitary and increased kinin production (as in Viper bite).

- Viper bites are associated with severe local pain, swelling, formation of blisters and necrosis.There may be associated discoloration of skin due to haemorthage and it may progress to involve the whole of bitten limb.
- Viper venom induces coagulopathy and Platelet dysfunction, thus, leading to life threatening hemorrhagic manifestations.
- Rhabdomyolysis may be suspected if here is muscle Pain and swelling which can be seen with sea snake and viper bites. Local manifestations can be- seen with cobra bites also but are less common with krait bites.
- Both cobra and krait bite may cause progressive descending paralysis. Krait bite is often said to have delayed onset and prolonged duration of paralysis as compared to cobra bite.
- Overall, hemotoxic viper bite with hemorrhagic

manifestations or coagulation abnormalities constitutes the most common clinical situation for the devolpment of renal failure
- Renal manifestations range from asymptomatic renal abnormalities to devolpment of dailysis dependent acute kidney injury
- Frequency of proteinuria in published data varies from 4% to 50% .[21]Usually Proteinuria is subnephrotic and resolves with recovery.
- Incidence of hematuria can be as high as 35% and its degree depends on the severity of envenomation. Its primarily cause is coagulation abnormalities induced by hemotoxic snakebite[9]
- Intravascular hemolysis leading to hemoglobinuria in hemotoxic snake bite and rhabdomyolysis leading to myoglobinuria in myotoxic snake bite are important laboratory abnormalities; and are directly implicated as a cause of renal failure due to pigment nephropathy in such settings.[9]
- Acute kidney injury as a manifestation of snake bite envenomation is seen in 5% to 29%Patients.
- Renal failure may develop in absence of shock and is usually oliguric.

The onset of renal failure is between hours to few days after snake bite and it usually recovery within 3 weeks

If the patient does not show any sign of renal recovery by 3-4 weeks, it is likely that the underlying renal abnormality is cortical necrosis or tubulointerstitial nephritis with acute tubular necrosis or crescentic glomerulonephritis.
- Hemorrhagic manifestations and coagulation abnormalities have not been reported after bite of elapid snakes in South Asia[20]
- Bites due to most of the venomous snakes have been reported to cause renal failure,it is mainly secondary to hemotoxic or myotoxic snake bite envenomation. Russells ciper,sawscaled viper, green pit viper, hump- nosed pit viper and sea snake are the most commoj snakes associated with renal failure in asia with all five of them present in india and srilanka[7]

Management
First Aid
- Move away from the snake
- Gently wash the bite with soap and water
- Cover the bite with a clean, cool compress or moist dressing
- Remove any constrictive clothing like rings or watches
- Note any changes to the skin or swelling around the bite
- Monitor your breathing and heart rate

Medical Care
- Go to the emergency department
- Receive antivenom, which boosts your immune response
- Receive antibiotics to prevent or treat infections
- Receive pain medication

Prevention
- Educate children and young adults about snakebite hazards
- Encourage people to wear long pants and footwear
- Don't try to locate the snake if you don't know what it was

Additional tips Don't try to suck out the venom, Don't apply ice, and Don't apply a tourniquet.

There is an unmet need of improving the management of snake bite victims at field level so that mortality and sequealae can be minimized. There is an important role of the type of first aid received by the patient. The usual practices of tying a tight tourniquet, cutting the wound and suctioning it are contraindicated. Any form of wound manipulation is risky and should be discouraged. There is no role of any traditional method or remedy, The pressure immobilization technique described for neurotoxic elapid bites for search for a surrogate predictor of Snake bite mediated acute kidney injury this study was done in KIMS medical college, Amalapuram,

Aim
1. To evaluate the surrogate predictor of SAKI Patient required hemodialysis
2. To establish role of oxidative and carbonyl stress marker in SAKI patient

MATERIALS AND METHOD
All snake bite patient admitted and required haemodialysis from April 2019 to December 2024 in KIMS Medical college,Amalapuram were included. Acute kidney injury was diagnosed according to [22]RIFEL criteria.Patient were provided polyvalent ASV where needed according to standard protocol, Oxidative stress marker like advanced oxidation protein product(AOPP) and Carbonyl stress marker methyl glyoxal (MG) were measured consecutively in 58 SAKI patient requiring HD and compared with 35 normal subject.

RESULT
Among 205 pt received HD male female ratio 2.5:1 the mean age was 37.2yr (4-75) commonest site lower limb- 89%
- Oliguria and bleeding manifestation common presentation
- Hypotension in 78% cases, cellulitis and inflammation was found in about 135(65.8%) patients.
- About 57(27.8%) had disseminated intravascular coagulation (DIC)
- ASV was used in 22.5 +1.85 vial
- Median HD was required 3 sessions
- Mean hospital stay 12 days (2-36 days) Bite to HD initiation time was 3.3 days.
- 20(34.4%)patient died of 58(28.3%) young patient (less than 18Yr).
- About 45(77.6%) had cellulitis 31(53.4%) had shock and hypotension at initial presentation
- Bleeding manifestation was found in 47(81%) and 27(46.5%) had DIC
- Hypotension, DIC ,Bleeding manifestation and cellulitis/ sever inflammation were found to predict the surrogate outcome in univariate analysis.

In logistic regression analysis cellulites and severe inflammation (OR 2.729 C1 1.23-6.053, p= 0.012)and bleeding manifestation (OR2.78, CI 1.22-6.053, p=0.012) were confounding risk factor for adverse outcome of SAKI patients whereas DIC(OR 4.08, CI 1.927-8.678, p<0.001) and hypotension/Shock (OR3.156, CI= 1.535-6.487, p= 0.001) at initial presentation came out as
independent predictor of death.

MG, the marker of carbonyl stress was increased by 3.58 times when compared to normal subject(p<0.001), both oxidative and carbonyl stress leads to increased protein modification s indicated by raised AOPP. When the level of oxidative and carbonyl stress markers and protein modifications compared among the survived (N=39) and expired (n=21) only AOPP and MG were found to be significantly elevated in expired patients than the survived.

CONCLUSION
Venomous snake bite is a life threatening condition with high mortality. Early intervention and aggressive treatment is needed for a favorable outcome. Oxidative and carbonyl stress may play a crucial role in pathogenesis of acute kidney injury and MG and AOPP may be used as functional biomarker of renal clearance. Glutathione precursor, carbonyl compound quencher and antioxidant drugs may be

useful in preventing kidney injury.

Abbreviations

- SAKI- snake bite acute kidney injury
- HD-hemodialysis
- AOPP-Advanced oxidation protein product
- MG- methyl glyoxal
- DIC- disseminated intravascular coagulation
- OR- odds ratio
- CI- confidence interval
- P- probability

REFERENCES

1. WarrellDA.Snakebite.Lancet2010;375: 77-88.
2. Subhankar Sarkar et al. Pediatr Nephrol. 2021Dec.
3. Lu Q, Clemetson JM, Clemetson KJ. Snake venoms and hemostasis. JThromb Haemost2005;3:1791-9.
4. Rocha ESM, Beraldo WT, Rosenfeld G. Bradykinin, a hypotensive and smooth musclestimulating factor released from plasma globulin by snake venoms and by trypsin. Am J Physiol1949;156:261-73.
5. Ducancel F. Endothelin-like peptides. Cell Mol Life Sci 2005;62:2828-39.
6. Lisy O, Huntley BK, McCormick DJ, Kurlansky PA, Burnett JC, Jr. Design, synthesis, and actions of a novel chimeric natriuretic peptide: CD-NP. J Am Coll Cardiol 2008;52:60-8.
7. K anjanabuch T, Sitprija V. Snakebite nephrotoxicity in Asia. Semin Nephrol 2008;28:363-72.
8. Vijeth SR, Dutta TK, Shahapurkar J. Correlation of renal status with hematologic profile in viperine bite. Am J Trop Med Hyg 1997;56:168-70.
9. Sitprija V. Snakebite nephropathy. Nephrology (Carlton) 2006;1 1:442-8.
10. Chugh KS, Singhal PC, Kher VK, Gupta VK, Malik GH, Narayan G, et al. Spectrum of acute cortical necrosis in Indian patients. Am J Med Sci 1983;286:10-20.
11. Sitprija V, BenyajatiC,Boonpucknavig V. Further observations of renal insufficiency in snakebite. Nephron 1974;13:396-403.
12. World J nephrol 2017 may6 , **Clinicopathological spectrum of snake bite-induced acute kidney injury from India,**https://doi.org/10.5527/wjn.v6.i3.150
13. Taylor and francis volume34,2012 ,long term renal outcome of snake bite and acute kidney injury ,https://doi.org/10.3109/0886022X.2011.647297
14. N Am J med sci , **Clinical Predictors of Acute Kidney Injury Following Snake Bite Envenomation,**https://doi.org/10.4103/1947-2714.120795
15. Kidney int rep,**Snake Envenoming An Underreported Cause of Acute Kidney Injury** ,https://doi.org/10.1016/j.ekir.2019.03.014
16. Grenvik AKE, Ayers SM, Holbrook PR, Shoemaker WC (editors). Injuries by venomous and poisonous animals. In: Textbook of Critical Care 4th ed 2000: I: 224-233
17. Reid HA, Theakston RBG. The Management of Snakebite. Bull of WHO. 1983;61(6):885-895
18. Weatherall DJ, Ledingham JGG, Warrell DA, editors. 3rd ed. I. Oxford Medical Publications;1996. Injuries, envenoming, poisoning, and allergic reactions caused by animals; pp. 1126-1139. (Oxford Textbook of Medicine).
19. Parikh CK. Parikh's Textbook of MedicalJurisprudence.1985:780-802.
20. AlirolE, Sharma SK, Bawaskar HS, Kuch U, Chappuis F. Snake Bite in South Asia: A Review.PLoS Negl Trop Dis 2010;4:e603.
21. Tin Nu S, Tin T, Myint L, Thein T, Tun P, Robertson JI, et al. Renal ischaemia, transient glomerular leak and acute renal tubular damage in patients envenomed by Russell's vipers(Daboia russeli siamensis) in Myanmar. Trans R Soc Trop Med Hyg 1993;87:678-81.
22. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative Workgroup. Acute renal failure – Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12.