Abstract

Snake bite is an important health concern in India as the country faces the highest burden of this occupational hazard worldwide. The spectrum of presentation may vary from mild local symptoms to rapid envenomation leading to sudden death. Acute kidney injury is an important consequence of snake bite and its proper supportive management after antivenom administration is of utmost importance for good patient outcome. It is usually reversible but acute cortical necrosis can occur leading to incomplete recovery. Differences in the types of snakes, their venom composition and effects, and bite specific characteristics necessitate development of local diagnostic and management protocols so that the already scarce health care resources are properly utilized and treatment can be optimized.
Introduction

Snake bite induced morbidity and mortality is a common health care problem all over the world especially in tropical and sub-tropical areas. Snake bite is an important environmental and occupational hazard. The involvement of predominantly young, healthy working population in poor rural areas compounded by lack of access to health care services in these areas signifies the social and economic impact of this problem. The poor health care infrastructure and lack of disease registries in areas where this problem is most frequently seen prevents an assessment of true burden. The most comprehensive effort in this regard estimates that about 421,000 envenomations and 20,000 deaths related to snake bite occur annually worldwide.\(^1\) The cautious approach in giving these estimates is reflected in the fact that the authors have themselves reported that these estimates are conservative and that the actual figures may be high as 1,841,000 envenomations and 94,000 deaths occurring annually. South Asia especially South East Asia and East Sub-Saharan Africa account for the highest burden of snakebite related envenomations in the world. The most conservative country specific estimates put India on top with maximum number of snake bite related envenomations and deaths in a year. About 19.2 % and 55% of all snake bite related envenomations and deaths, respectively, that occur annually all over the world take place in India.\(^1\)

A recently published survey of snake bite related mortality in India estimates that 45,900 deaths occur annually in India due to snake bite. The states of Uttar Pradesh, Andhra Pradesh and Bihar share the highest burden of this mortality. Majority of deaths occurred in rural areas during monsoon season and involved young males.\(^2\)

Only about one fifth of the >3000 species of snakes that are found worldwide are poisonous. The most conservative estimate of all snake bites (both with envenomation and without envenomation) is 1,200,000 to 5,500,000 snakebites occurring globally every year\(^1\). It is estimated that 18% of the total snake bites in India present with some form of envenomation.\(^1\) The relationship between the total number of snake bites and those with envenomation is highly variable across the world. A rough estimate in this regard puts the total number of snake bites at about three times that of venomous bites.\(^2\)

Worldwide, the major families of venomous snakes are viperidae, elapidae, colubridae, hydrophidae and atractaspididae.\(^3-5\) Usually, elapids are neurotoxic, vipers are hemotoxic and hydrophids are myotoxic. However, it should be remembered that these effects are not mutually exclusive. The distribution of various types of venomous snakes in different parts of the world is different and therefore, the clinical manifestations and type of antivenom treatment also differ accordingly. In addition, differences in clinical manifestations of bite due to same species in different geographical regions have also been seen and attributed to variations in type of venom.\(^4\) As the true species identification of the venomous snake that has bitten the patient is not possible in majority of the cases, antivenom prepared by using the venom of commonly prevalent venomous species in a particular region is used.
The concept of venomous snakes in India has traditionally revolved around four main species. These are Russell’s viper (Daboia russelii), the saw-scaled viper (Echis carinatus), the Indian or spectacled cobra (Naja naja), and the common krait (Bungarus caeruleus). Though highly toxic, the number of bites with king cobra (Ophiophagus hannah) leading to fatal outcomes are relatively negligible. Recently, hump-nosed pit viper (Hypnale hypnale) has also been identified as a cause of severe systemic envenomation. A list of medically important venomous snakes in India is given in table 1.

Table 1: Medically important venomous snakes in India

<table>
<thead>
<tr>
<th>Viperidae</th>
<th>Elapidae</th>
<th>Hydrophidae</th>
</tr>
</thead>
</table>
| • Russell’s viper (Daboia russelii) | • Indian or spectacled cobra (Naja naja) | *Adapted from Pathophysiology*
| • Saw-scaled viper (Echis carinatus) | • Common krait (Bungarus caeruleus) | Health Sciences 2012;1(2):JS007 3
| • Hump-nosed pit viper (Hypnale hypnale) | • King cobra (Ophiophagus hannah) | An Open Access Peer Reviewed E-Journal
| • White lipped pit viper (Trimeresurus albolabris) |                                    |

Pathophysiology

The complex nature of snake venom is responsible for the wide variety of effects seen in snake bite patients. More than 100 different kinds of peptides or proteins, lipids, amines, carbohydrates etc. have been isolated from snake venoms, not all of which are toxic to humans. Activation or inhibition of various coagulation proteins or platelets, and endothelial disruption caused by phospholipases, serine proteases, metalloproteinases, disintegrins and C-type lectins lead to coagulopathy. Hemorrhagins lead to spontaneous bleeding by directly injuring the vascular endothelium. Digestive hydrolases, hyaluronidase, and polypeptide cytotoxins contribute to the local tissue necrosis seen after bites of some snakes. 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 envenomation potentiate the cascade of events leading to further deterioration.

Permeability factors that increase extravasation of plasma from intravascular compartment, and direct and indirect effects on cardiac muscle and vascular smooth muscle can lead to hypotension without any bleeding manifestations.
Oligopeptides potentiating bradykinin action, sarafotoxins bearing homology to endothelin, vascular endothelial growth factor and natriuretic peptides are examples of such toxins seen in snake venom.11-13 Neurotoxins impair transmission at neuromuscular junction by acting either pre synaptically or post synaptically.

Experimental evidence suggests that the hemodynamic response to venomous snake bite especially hemotoxic viper bite is similar to sepsis and that altered renal hemodynamics (increased renal vascular resistance with decreased renal blood flow and decreased glomerular filtration rate) are probably central to pathogenesis of renal failure.14 Hemorrhage leading to intravascular volume depletion, hemolysis, rhabdomyolysis and disseminated intravascular coagulation are other factors involved in pathogenesis (Table 2). There seems to be a good correlation between the degree of renal failure and hemotoxic and myotoxic actions of snake venom.16

| Disseminated intravascular coagulation |
| Direct nephrotoxicity of venom |

*Adapted from

The occasional occurrence of renal failure in a patient without above mentioned pathological factors points towards direct nephrotoxic potential of snake venom.14 Both structural and functional changes in cells of glomerulus, proximal tubules, distal tubules and vascular endothelium have been seen in experimental models of snake bite related acute renal failure.14 Immunological mechanisms leading to renal involvement like immune complex glomerulonephritis probably have a very minor role.

It is important to remember that the great diversity in snake population, venom constituents and effects of venom in victims reflect the complex mechanisms involved and stress upon the need of individualizing patient management.

Clinical manifestations

Snake bite is a frightening accident whenever it happens. The facts that majority of the snakes are non-venomous and that not all bites by a venomous snake involve injection of venom, lead to a very complicated situation. The sudden panic leading to chaotic and often harmful responses by patients or attendants, together with lack of species identification pose a very difficult diagnostic situation for treating clinician. This is further compounded by lack of diagnostic facilities and anti venom supplies in far flung rural areas which are most affected by this problem. Though not fool proof, a syndromic approach proposed previously may be
This approach can help the treating physician in ascertaining the type of snake involved in India (Figure 1).

Figure 1: Type of snake bite envenomation based on clinical presentation in India

A. Presence of local symptoms
B. Absent or minimal local symptoms

- Absent or Minimal local envenomation symptoms like swelling etc.
  - Neuroparalytic symptoms
    - Present
      - Bite on land
        - Krait bite
      - Bite in sea
        - Sea snake
    - Absent
      - History of cola colored urine or Renal failure
      - Prolonged 20 minutes WBCT or Bleeding manifestations

WBCT: Whole blood clotting time
*Adapted from .
Viper bites are associated with profound local pain, swelling, formation of blisters and development of necrosis. There may be associated discoloration of skin due to haemorrhage 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 at various sites in the body. Presence of muscle pains and swelling may suggest rhabdomyolysis 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. However, both cobra and krait have pronounced neurologic manifestations in the form of progressive descending paralysis. Envenomation after krait bite is often said to have delayed onset and prolonged duration of paralysis as compared to cobra bite. It is important to note that hemorrhagic manifestations and coagulation abnormalities have not been reported after bite of elapid snakes in South Asia. Some venomous species like cobra are good swimmers and can also bite humans in ponds, rivers etc.

Although 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. Russell’s viper, saw-scaled viper, green pit viper, hump-nosed pit viper and sea snake are the most common snakes associated with renal failure in Asia with all five of them present in India and Sri Lanka. Overall, hemotoxic viper bite with hemorrhagic manifestations or coagulation abnormalities constitutes the most common clinical situation for the development of renal failure. The renal manifestations range from asymptomatic renal abnormalities to development of dialysis dependent acute kidney injury.

The frequency of proteinuria in published data varies from 4% in Thailand to 50% in Myanmar. Proteinuria is usually subnephrotic and resolves with recovery. The incidence of hematuria can be as high as 35% and its degree depends on the severity of envenomation. It is primarily caused due to coagulation abnormalities induced by hemotoxic snake bite. 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.

Acute kidney injury as a manifestation of snake bite envenomation is seen in 5% to 29% of the patients. This variation is again due to differences in the type of snakes and degree of envenomation. At a poison control centre in a tertiary care hospital in South India, snake bites accounted for three fourth of all cases of poisoning related related acute kidney injuries. Hemorrhagic manifestations leading to hypotension and shock, intravascular hemolysis, disseminated intravascular coagulation or rhabdomyolysis are usually present. The 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 will recover 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.\textsuperscript{14} A variety of histopathological findings have been described in snake bite patients (Table 3). The most common of them are tubulointerstitial lesions and amongst them, a large majority would have acute tubular necrosis.\textsuperscript{4} Severe tubular and vascular lesions, increased rates of apoptosis in distal tubular epithelial cells, and presence of eosinophils, mast cells and hyperplastic fibroblasts in the interstitium are some of the features which are prominent in snake bite induced acute tubular necrosis as compared to other common causes of acute tubular necrosis.\textsuperscript{22} Acute interstitial nephritis has also been reported.\textsuperscript{26} Severe form of glomerular involvement is very rare and may include crescentic glomerulonephritis or diffuse proliferative glomerulonephritis.\textsuperscript{15} Vasculitis in the literature.\textsuperscript{27} Acute cortical necrosis, patchy or diffuse, is the most dreaded histopathological finding as it confers very poor renal survival.\textsuperscript{4} It is associated with evidence of disseminated intravascular coagulation. For unknown reasons, the incidence of acute cortical necrosis is more in India as compared to other South Asian countries. Also, snake bite is the second most common cause of acute cortical necrosis in India.\textsuperscript{23} The significance of glomerular lesions observed in patients with snake bite is uncertain.\textsuperscript{4} Primary glomerular involvement is uncommon in snake bite envenomation. The experimental data in this regard suggests that perhaps mesangiolysis is an early and most consistent abnormality associated with snake bite envenomation.\textsuperscript{2} Mild focal and segmental mesangial proliferation is the most common lesion in human patients.\textsuperscript{14} Severe form of glomerular involvement is very rare and may include crescentic glomerulonephritis or diffuse proliferative glomerulonephritis.\textsuperscript{15} A clinicopathological correlation between histological findings and clinical presentation has also been proposed.\textsuperscript{22} A clinicopathological correlation between histological findings and clinical presentation has also been proposed.\textsuperscript{22}

**Table 3: Morphological pattern of injury in acute renal failure**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute tubular necrosis*</td>
<td>Most common, usually co-exists with other forms of injury</td>
</tr>
<tr>
<td>Acute diffuse interstitial nephritis#</td>
<td>Uncommon, associated with prolonged clinical course</td>
</tr>
<tr>
<td>Acute cortical necrosis$</td>
<td>Most commonly associated with incomplete or no recovery</td>
</tr>
<tr>
<td>Vasculitis#</td>
<td></td>
</tr>
<tr>
<td>Extracapillary proliferative (Crescentic) glomerulonephritis#</td>
<td></td>
</tr>
</tbody>
</table>

\* Most common, usually co-exists with other forms of injury  
\# Uncommon, associated with prolonged clinical course  
\$ Most commonly associated with incomplete or no recovery  
\textsuperscript{Adapted from}

**Management**

There is an unmet need of improving the management of snake bite victims at field level so that mortality and sequelae 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...
has been said to be impractical in Indian field conditions and is not recommended in India. The best way is to reassure the patient, immobilize him completely and transfer to the nearest health care facility as soon as possible. If the snake has been killed and brought to health care facility, an attempt should be made to identify the species; but it should not be done at the cost of patient management. Immunodiagnosis by detection of snake venom antigens in victim’s blood or tissue fluids is commercially available in some countries like Australia but is currently impractical in Indian context. All suspected snake bite patients should be observed for at least 24 hours before they are discharged.

After ensuring stability of vital parameters, booster dose of tetanus toxoid injection should be given if there is no evidence of coagulopathy. Antibiotics may be needed only if there is associated necrosis or cellulitis. There is no evidence to suggest that routine use of antibiotics is helpful in local swelling after snake bite. Pain relief should be achieved with paracetamol or opioids like tramadol. Aspirin or other non steroidal anti inflammatory drugs are contraindicated in hemotoxic snake bites because they may adversely affect the coagulation.

Antivenom is the most important and specific treatment for the management of snake bite. It should be administered as soon as possible whenever indicated. Polyvalent antivenom is available in India which neutralizes the venom of Russell’s viper (Daboia russelii), saw-scaled viper (Echis carinatus), Indian or spectacled cobra (Naja naja), and common krait (Bungarus caeruleus). The initial dose of antivenom should be 10 vials (one vial is reconstituted to 10 ml of solution). Hemorrhagic manifestations, prolonged 20 minutes whole blood clotting time, neuroparalytic manifestations and symptoms of severe local envenomation (rapidly progressing, involving more than half of limb) are the usual indications for antivenom administration (Table 4). Repeat doses of antivenom should depend on patient’s envenomation symptoms, monitoring test results and clinical situation. It is likely that there will be no additional benefit of more than 20 total vials of antivenom in neurotoxic snake bites and repeat dose, if needed, is administered after 1-2 hours of observation. In hemotoxic snake bite, a maximum total dose of 30 vials should suffice and repeat doses are given after every 6 hours interval if there is persistent coagulopathy. The temptation to give continued high doses of already scarce antivenom should be resisted. Venomous snake bites by other snakes against whom the polyvalent antivenom is not effective has been described and may be the cause of apparent lack of efficacy of antivenom treatment in some cases. Patients who respond favourably to antivenom administration with reversal of signs should be monitored for recurrent envenomation that has been occasionally described and attributed to venom redistribution, continued absorption from bite site or dissociation of venom-antivenom complex.
Table 4: Indications for antivenom administration in snake bite patients*

<table>
<thead>
<tr>
<th>Local envenomation</th>
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<tbody>
<tr>
<td>• Severe swelling involving more than half of bitten limb (exclude effect of tight tourniquets if used)</td>
<td></td>
</tr>
<tr>
<td>• Rapid progression of swelling beyond wrist or ankle within few hours</td>
<td></td>
</tr>
<tr>
<td>• Severe swelling of bitten finger or toe with necrosis</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Systemic envenomation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Coagulopathy</td>
<td></td>
</tr>
<tr>
<td>o Bleeding manifestations</td>
<td></td>
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<tr>
<td>o Prolonged 20 minutes whole blood clotting time</td>
<td></td>
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<tr>
<td>• Neuroparalytic</td>
<td></td>
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<tr>
<td>o Ptosis</td>
<td></td>
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<tr>
<td>o Ophthalmoplegia</td>
<td></td>
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<tr>
<td>o Muscular paralysis, inability to hold neck</td>
<td></td>
</tr>
<tr>
<td>• Unexplained shock, respiratory failure</td>
<td></td>
</tr>
<tr>
<td>• Acute kidney injury</td>
<td></td>
</tr>
<tr>
<td>• Clinical or laboratory evidence of hemolysis or rhabdomyolysis</td>
<td></td>
</tr>
<tr>
<td>• Recurrent envenomation after initial improvement with antivenom</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from

There is no role for local administration of antivenom at the site of bite. There is a risk of adverse reactions with antivenom administration but they can be managed and should not delay the administration of antivenom. No prior skin testing is required before antivenom administration. In patients with no indication for antivenom treatment at presentation, careful reassessment of clinical condition and laboratory parameters (20 minutes whole blood clotting time) every 30 minutes should continue for first 3 hours and every hour beyond 3 hours.

Hypotension and shock should be aggressively managed with intravenous fluids and blood transfusions. Urinary alkalization may be done in cases of hemolysis or rhabdomyolysis. The management of acute kidney injury in snake bite patients is essentially the same as in other acute kidney injury patients. The increased risk of hyperkalemia in the setting of hemolysis or rhabdomyolysis and need of proper fluid balance management with transfusion may necessitate more rigorous monitoring and more frequent need of dialysis to manage complications. Dialysis may be given either as hemodialysis or peritoneal dialysis. Incomplete or no recovery of renal function even after 3-4 weeks would suggest most commonly acute cortical necrosis and may require renal biopsy for diagnosis if contrast enhanced computed tomographic scan is inconclusive.

Any surgical intervention should be undertaken only after the coagulation disturbances have been corrected. Fasciotomy for presumed compartment syndrome can be justified only after objective measurement of intracompartmental pressure confirms it. A trial of anticholinesterase drugs like edrophonium or neostigmine should be given in neurotoxic envenomation but no repeat doses are recommended in the absence of any initial improvement. The most important treatment for coagulopathy after snake bite is antivenom. After antivenom administration; whole blood, fresh frozen plasma, cryoprecipitate or platelet concentrate transfusions are required only if
there is severe bleeding or urgent need of surgery.\textsuperscript{13}

A number of preventive measures have been advocated like using footwear that covers whole of feet, covering other exposed areas of body while working, not sleeping on ground, using lights in the dark, and keeping animal feeds, rodents and rubbish away from human dwellings.\textsuperscript{20}

Snake bite is still considered a neglected health problem despite advances in its understanding and management strategies.\textsuperscript{2} In spite of being one of the largest producers of antivenom worldwide; the burden of disease and lack of proper management leave a wide scope for improving the outcomes of snake bite related morbidity and mortality in India \textsuperscript{31}.

References


13. Lisy O, Huntley BK, McCormick DJ, Kurlansky PA, Burnett JC, Jr. Design, synthesis, and actions of a novel


