

Management of Snake Bite in India - Revisited

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Around 1841000 envenomings and 94000 deaths globally are predicted by WHO, with India having the worst snakebite problem in the world. (1-4) Indian states with high incidence of snakebites are Tamil Nadu, West Bengal, Maharashtra, Uttar Pradesh, and Kerala. (5) Out of 256 species of snakes found in India, 52 are poisonous (6). Maximum mortality due to poisonous snake bite in India occurs due to the "Big 4" species i.e. the Indian cobra (*Naja naja*), the common krait (*Bungarus caeruleus*), the Russell's viper (*Daboia russelii*) and the saw-scaled viper (*Echis carinatus*). Besides these there are about 7 poisonous coral snakes and 29 highly poisonous sea snakes.

Recently, hump-nosed pit viper (*Hypnale hypnale*), was found to be poisonous. Earlier its poisonous nature was concealed by its misidentification as the saw-scaled viper. (7,8) Ineffectiveness of polyvalent ASV in cases of Sochurek's saw-scaled viper (*Echis carinatus sochureki*) in Rajasthan has raised doubts about use of polyvalent ASV in all cases. (8) Such findings have rendered the "Big 4" theory outdated. (9) There is need to approach the snake bite issue with regards to development of species specific monovalent anti snake venoms (ASV), as well as identification of other not yet recognised poisonous species in India. Snakebites show a classical seasonal variation, being more common in summers and rainy season. [2] Farmers, herders, hunters & fishermen are more predisposed to snakebite and majority of bites are provoked. Children due to inquisitiveness and smaller size are more prone to suffer. Nearly 75% of snake bites occur in outdoor and 75-90% in rural settings. (10,11) Males are bitten twice as often as females, (3) Most frequent site of bite are lower limbs (2/3rd) of which 50% occur in feet alone. (12-14) The percentage of dry bites ranges from 10-80% for various poisonous snakes. (15) The snake bites are common in daytime in South India and nocturnal in some North Indian areas. Maximum incidence is between 4.00 pm to midnight, during rainfall, after floods and natural disaster.

Pathophysiology of Snake Venom:-Snake venom is mixture of enzymatic & nonenzymatic compound, nontoxic proteins including carbohydrates & metals.

Components of snake venom include about (a) 20 different kinds of enzymes including phospholipase, A2 B, C, D, hydrolases, phosphatases, proteases, esterase, acetyl choline esterase, transaminase, hyaluronidase, phosphodiesterase, DNase and RNase as well as (b) Nonenzymatic compounds e.g. Neurotoxins and haemorrhagins. From therapeutic point of view, species of snakes are generally classified according to predominant component of toxins in their venom e.g.

(a) Cobra venom contains neurotoxins (e.g. Cobrotoxin and Bungarotoxin) causing post synaptic blockage as well as it has cardiotoxin. (b) Viper contains acetylcho and vasculotoxins disturbing coagulation pathways. l inesterase.

(c) Krait venom contains neurotoxin (Bungarotoxin B) which results in presynaptic blockage.

(d) Other products like hemorrhagin, myotoxins, nephrotoxin cause effects upon vascular endothelium, muscle necrosis, myoglobinuria, hyperkalemia, renal injury, DIC and rhabdomyolysis.

(e) Proteolysis damages RBCs, WBCs, platelet membranes and vascular endothelial membrane and causes increased vascular permeability. This manifests as edema, inflammation, hypoalbuminemia, hypotension and shock.

(f) Local Effects of Venom occur due to protease, phospholipase 2, polypeptide toxin, hyaluronidase, histamine and bradykinin etc resulting in local pain, edema, bullae formation, necrosis and gangrene etc.

Clinical Features: Snake bite victims develop varied symptoms and signs due to anxiety and fear. Patients may develop paraesthesia, and carpedal spasm due to hyperventilation. Some may develop syncope, vasovagal shock and may even collapse. (16) Clinical presentation of a snakebite victim varies with age and size of the patient, the species of snake, number and location of bite, the quantity and toxicity of venom. The children generally receive larger envenomation dose relative to body size. (17)

I. *Snake bite without manifestations:* Confirmed bites without manifestations may be either due to poisonous dry bites or bite by non poisonous snake.

II. *Local manifestations:* It manifests as pain,

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tenderness paraesthesia at local site followed by swelling of bitten limb (upto half the size of limb in severe local reaction) and bullae formation. Local bleeding, petechiae and echymotic lesions and regional lymphadenopathy follows. Severe limb pain, absence of arterial pulse and cold limb may be suggestive of intercompartment syndrome and may further lead to Raynaud's phenomenon and gangrene due to arterial thrombosis. Other complications like secondary infections and tetanus and gas gangrene may also develop.

III. *Systemic Manifestations like marked agitation, flight and fear of impending death* enhance systemic absorption of venom. Fear may cause transient pallor, sweating & vomiting.

a) Neurotoxic features set in within 6 hrs but may be delayed and include: (i) Pre paralytic syndrome in form of vomiting blurred vision, drowsiness, heaviness of head, and tingling sensation of mouth. (ii) Paralysis first appears as bilateral ptosis followed sequentially by bilateral ophthalmoplegia, paralysis of muscles of palate jaw, tongue, larynx, neck and muscles of deglutition. Muscles innervated by cranial nerves are involved earlier. Reflexes and pupillary reaction to light are usually preserved till late stages. Muscles of diaphragm are involved late accounting for terminal respiratory paralysis. Onset of coma is variable and victim may progress to coma in 2hrs. (18)

b) Cardiotoxic features include tachycardia, hypotension, & ECG changes. 25% of viper bites include fluctuations in cardiac rate, rhythm, blood pressure. Myocardial infarction and sudden cardiac arrest may occur due to dyselectrolytemia.

c) Haemostatic abnormalities manifest as bleeding from the wound, gum and other sites. Extensive bleeding resulting in hypotension and shock, intracerebral and subarachnoid haemorrhage may occur due to consumption coagulopathy & haemorrhagins.

d) Nephrotoxicity may persist even after correction of coagulation defects and may be suggestive of multifactorial venom induced renal failure.

e) Hypotension syndromes due to increased capillary permeability manifests as serous effusions/ pulmonary edema/ haemoconcentration / hypoalbuminemia and shock.

f) Pregnancy outcomes are grave with either abortion or antepartum or postpartum hemorrhage.

g) Rare outcomes include hypopituitarism, bilateral thalamic haematoma, and hysteric paralysis.

Late-onset envenoming: The patient of snake bite has to be observed for at least 24 hours. Late manifestations of envenomation up to 6-12 hours are well

documented in the Krait and the Hump-nosed pit viper. (19-21) Younger snakes in rainy season tend to bite in foot, which having harder tissue tends to delay signs of envenomation.

Lab diagnosis: (1) 20-min whole blood clotting test (20 WBCT) a bedside test of coagulopathy to diagnose viper and rule out elapid bite. Elapids do not cause anti hemostatic symptoms. (22)

(2) Enzyme linked immunosorbent assay (ELISA) for species identification. (23)

(3) Hemogram: (a) Hemoconcentration due to increased capillary leak (b) Anemia due to hemolysis (c) Neutrophilic leucocytosis signifies systemic absorption of venom (16) and (d) Thrombocytopenia in viper envenomation.

(4) Serum Biochemistry (a) S Creatinine to rule out renal failure. (b) Serum Amylase (c) Elevated S Creatinine Phosphokinase (CPK) suggests muscle damage (d) Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are prolonged in viper bite. (e) Low Fibrinogen and raised fibrin degradation products (FDPs) are found in case of interference with the clotting mechanism. (f) Electrolytes.

(5) Arterial blood gas

(6) Urine examination: may reveals hematuria, proteinuria, hemoglobinuria, or myoglobinuria.

(7) Nonspecific ECG changes like bradycardia and atrioventricular block with ST-T changes may be seen. (24)

(8) EEG abnormalities without association with encephalopathy have been noted in up to 96% of cases, seen mainly in the temporal lobes. (25)

(9) Blood grouping, typing and cross-matching as both venom and ASV can interfere with cross-matching.

Management: (28) Aim of the first aid is to reduce systemic absorption of venom and prevent life-threatening complications. No incisions in places where the bite is located, as excessive bleeding and the risk of infection are favored. Do not use tourniquets since they hinder blood flow and therefore cause more tissue damage. Do not apply ice; it worsens local lesions caused by poison. Do not administer electric shocks of any kind. Do not use any chemicals or extracts of plants or animals of any kind, so far none have been proven scientifically effective as treatment. Do not give alcoholic beverages. Do not suction with the mouth, this favors infections on the bite site and can be dangerous if you have a cavity or open lesion in your mouth. In addition there is no guarantee of how much venom you can withdraw with this method.

It is however helpful to note the approximate time of bite as it helps in deciding severity of envenomation.

Hospital treatment: Severe envenomation usually

requires ICU care as it may lead to respiratory paralysis, hypotension, pulmonary edema, syncope and coma. Supportive therapy is required to buy time while the damaged organs recover. Presence of fang marks with moderate pain, local edema, erythema, ecchymosis, and no systemic reactions can be treated in ward under close monitoring.

Emergency care: Initial victim evaluation include state of airway, breathing, circulatory status, and consciousness. Actual measurement of pressure prior to fasciotomy is necessary otherwise the patient may bleed to death. Urgent resuscitation is prerequisite in victim with shock, respiratory failure and cardiac arrest. It may include:-

(A) Oxygen therapy and intravenous access with a large-bore intravenous catheter are a priority. A bolus of normal saline or Ringer's lactate should be given to all patients with suspected envenomation.

(B) Tourniquets though no more recommended, are still used extensively because of lack of awareness. Sudden removal of tourniquet leads to a massive surge of venom. Check for pulse distal to tourniquet. Apply BP cuff with pressure and slowly release it to prevent sudden release of high dose of venom in circulation and its complications. (26)

(C) If the victim has brought the snake, try identifying the species carefully, since crotalids can envenomate even when dead.

Specific Therapy: Anti-snake venom (ASV) is the mainstay of treatment. In India, polyvalent ASV is prepared by Central Research Institute, Kasauli (HP) and the Haffkine Corporation, Parel (Mumbai). Monovalent ASV is not available in India. As per WHO recommendation, the most effective treatment for snakebite is the administration of monovalent ASV (27); however, this is not always available because of its high cost, nonavailability, and difficulty in identifying the snake. (2) ASV Administration Criteria as per National protocol 2008 in Indian context is as following (28). It should be administered if there is significant envenomation i.e. incoagulable blood shown by the 20WBCT or significant limb swelling for viperine bite, neurological signs for elapidae bite.

ASV Dosage & Repeat Dosage: Dosing is based on the degree of envenomation. Current recommendations of ASV doses are (28) as following :-
(a) Initial dose: The recommended initial dose of ASV is 8-10 vials administered over 1 hour, administered either as IV infusion in D2 5 W or normal saline, at the rate of 5-10 ml/kg body weight or as slow IV injection as 2 ml/minute.

(b) Mild Envenomation :(Neurotoxic/ hemotoxic

symptoms appearing > 3 hours after bite), administer 8 vials of ASV.

(c) Severe envenomation (symptoms appearing within 3 hours after bite) 8-10 vials.

Dose of ASV does not vary with age of victim. ASV should ideally be administered within 4 hours of bite, but is effective even if given within 24 h. ASV neutralizes only unbound, free flowing venom. As it carries risk of anaphylaxis, epinephrine should thus be kept ready.

Mode of administration is IV only. In case of life saving surgery dose of ASV up to 25 vials is justified. (26) ASV dose in case of snakes injecting massive amounts of venom, e.g. King cobra or Australian elapids, massive doses even up to 50-100 vials are required. ASV should not be locally infiltrated around bite mark, as it may result in severe pain and increase in intra-compartmental pressure. Intramuscular injections are also not preferred due to poor bioavailability of ASV by this route. Other side effects include pain on injection site, hematoma formation and sciatic nerve damage. Repeat doses for haemotoxic species is based on the 6 hour rule. Repeat doses for neurotoxin are based on the 1-2 hour rule. (16) The maximum recommended dose for haemotoxic bites is 30 vials of ASV. The maximum recommended dose for neurotoxic bites is 20 vials of ASV. (Table-1)

Response to ASV is marked by normalization of blood pressure. While bleeding may stop 15-30 minutes after ASV administration, coagulation disturbances take up to 6 hours to normalize. Neurotoxicity starts improving within 30 min, but complete recovery may take 24-48 hours.

Victims Who Arrive Late: In India, the victim may arrive several days after the bite with acute renal failure or respiratory failure. The key factor to decide on ASV treatment is presence of current venom activity by 20 WBCT. If coagulopathy is present administer ASV, otherwise treat renal failure. In case of neurotoxicity it is wiser to administer of 8-10 vials of ASV to ensure that no unbound venom is present.

Reactions to ASV

(a) Early anaphylactic reactions occurs within 10-180 min of initiating therapy

(b) Pyrogenic reactions usually develop 1-2 h after treatment.

(c) Late (serum sickness-type) reactions develop 1-12 (mean 7) days after treatment.

Treatment of ASV reactions

Immediately withhold ASV administration temporarily and start adrenaline (1 in 1000) given intramuscularly in an initial dose of 0.5 mg in adults or 0.01 mg/kg body weight in children. The dose can be repeated every 5-10

Table.1 Usual Dose of Envenomation By Bite of Different Species of Snakes.

Species of snake	Dose of venom inoculation	Vials ASV Required
Naja naja	211.3	35.0
Cobra	60	15
Common krait	5.4	1.0
Russell's Viper	63.0	15.0
Saw scaled Viper	13.0	8.0
Ophlophagus hannah	100.0	12.0

1 ml of Polyvalent ASV neutralizes about 0.6 mg of venom; one vial 10 ml of ASV will neutralize 6 mg of venom. Therefore approximate dose of ASV for Naja naja bite will be about 211.3/0.6 ie 330 ml of ASV ie about 33 vials. Incase of common krait dose will be 5.4/0.6 ie 6ml, in case of Russell's viper about 120 ml (10-12 vials) and so on. (34-37) As snakes inject the same amount of venom into children and adults, dosage in children remains same as adults.(38) In fact degree of envenomation is more severe in children due to less body mass while the dose of venom received is same as an adult.

min if necessary. After adrenaline, an anti-H1 antihistamine such as chlorpheniramine maleate (adult dose 10 mg, children 0.2 mg/kg) should be given intravenously. It may be followed by intravenous hydrocortisone (adult dose 100 mg, children 2 mg/kg). (29). Late (serum sickness-type) reactions usually respond to a 5-day course of oral antihistamine (e.g., chlorpheniramine 2 mg six hourly in adults and 0.25 mg/kg/day in divided doses in children). Patients who fail to respond within 24-48 h should be given a 5-day course of prednisolone (5 mg six hourly in adults and 0.7 mg/kg/day in divided doses in children).

Role of prophylaxis for ASV reactions is controversial. There are no systematic trials of sufficient power to show that prophylactic regimes are effective in preventing ASV reactions which may occur in about 20% patients treated with ASV.

Recovery Phase: Following adequate dose of ASV, the following responses may be seen:
a) Cessation of spontaneous bleeding within 15-30 min.
b) Blood coagulability normalises in 6 hours.
c) Post synaptic neurotoxic envenoming such as the Cobra may begin to improve as early as 30 minutes after antivenom, but can take several hours.
d) Presynaptic neurotoxic envenoming such as the Krait usually takes a considerable time to improve reflecting the need for the body to generate new acetylcholine emitters.e) Active haemolysis and rhabdomyolysis may cease within a few hours and the urine returns to its

normal colour. (f) In shocked patients, blood pressure may increase after 30 minutes.

Supportive therapy is required to buy time while the damaged organs recover. The type of supportive care that may be needed is summarized below.

Coagulopathy with bleeding usually reverses after ASV treatment. Sometimes fresh frozen plasma, cryoprecipitate (fibrinogen, factor VIII), fresh whole blood, or platelet concentrates may be required. (30) The use of heparin and botropase for haemostasis heparin is doubtful role and thus not recommended. (31)

Neurotoxic symptoms:ASV therapy treatment alone cannot be relied upon to save the life of a patient with bulbar and respiratory paralysis. Loss of the gag reflex, failure to cough, or respiratory distress warrants endotracheal intubation and mechanical ventilation. Anticholinesterases like Neostigmine can be given in case of elapid toxin with features of myasthenia gravis. Neostigmine is particularly effective in postsynaptic neurotoxins such as those of cobra and is not useful against presynaptic neurotoxin i.e. common Krait and the Russell's viper. (32) Neostigmine test should be performed by administering 0.5-2 mg IV and if neurological improvement occurs, it should be continued 1/2 hourly over next 8 hours. It would perhaps be reasonable to offer anticholinesterase therapy to those who demonstrate a positive response to the tensilon test or a decremental response to repetitive nerve stimulation. Pain can be treated with paracetamol in adult dose of 500-1000mg 4-6 hourly and pediatric dose of 10mg/kg every 4-6 hourly orally. Aspirin and NSAIDs should not be used as they can aggravate the existing coagulopathy. Mild opiates such as Tramadol, 50 mg orally or IV can be used for relief of severe pain.Care of bitten part: - Fasciotomy should not be contemplated until complete hemostasis. It may worsen myonecrosis in crotalid snake venom-injected tissue. (33) Prophylactic course of penicillin (or erythromycin for penicillin-hypersensitive patients) will cover anaerobes in contaminated bite site. A booster dose of tetanus toxoid is recommended.

Conclusion

An early and adequate medical management of snake bite avoids prolonged hospitalization. Proper public education, correct first aid and early transfer to proper facility can help in reducing morbidity and mortality. Judicious use of ASV is necessary due to its short supply and its potentially dangerous reactions.

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