ABSTRACT

In India Antisnake venom (ASV) should be used in snakebite cases with features of systemic envenomation. Systemic spontaneous bleeding and 20 minutes whole blood clotting test (20WBCT) are bedside tests to know systemic envenomation in viper bite. Ptosis ophthalmoplegia and dysphagia are early manifestations suggestive of systemic envenomation in Elapidae bite. 100 ml of polyvalent ASV is the initial quantity of ASV required. Skin testing for detection of possible allergic reaction to ASV has not been recommended by WHO in view of its inability to predict the same. But close observations for 3 hrs with adrenaline injection ready to use is essential to combat any allergic reaction. Adrenaline 0.5 mg given intramuscularly is the drug of choice for ASV induced immediate hypersensitive reaction. Repeat dose of 100 ml ASV to be given to Elapidae bite after 1-2 hrs of first dose if there is no improvement in neurological manifestation or the condition deteriorated. In vipers bite repeat dose of 100 ml ASV to be given if 20 WBCT is abnormal after 6 hrs of initial therapy.

INTRODUCTION:

Snake bite is a major public health problem in India with estimated annual snake bite incidence is about 66-163/1 lakh population, morbidity about 1.4 to 68 / 1 lakh population, mortality about 1.1 to 2.4 / 1 lakh population and case fatality rate of 1.7 to 20%. It is estimated that between 35000 and 50000 people die of snake bite in India each year. Therefore, there is an urgent need to prevent death due to snakebite in India. Anti Snake Venom (ASV) and its rational use is the only definitive treatment to neutralise venom in circulation and in tissue fluid to save life in snake bite cases.

There are many causes attributed to high snake bite mortality. Lack of adequate training and knowledge of doctors in rational use of ASV is very important. Snakes are different in different geographical area having different clinical manifestation for which different ASV is used. Most of the important text books and Journals from western countries deal with snakes and snake bite of their country and not of India. In 1999 WHO has recommended a guideline for managing snake bite cases. In 2005 WHO has recommended a guideline for treating snake bite cases in South-East Asia which is not available in commonly used text book of medicine and even it is not mentioned in product information notes attached to ASV vials.

THE MEDICALLY IMPORTANT SNAKES OF INDIA (TABLE I)

Though there are nearly 15 species of poisonous snakes of medical importance in India; only 4 are most important:

i. Naja naja (common cobra)
ii. B. caeruleus (common krait)
iii. Daboia russelii (Russell’s viper)
iv. Echis carinatus (Saw-scaled viper)

The first two belongs to Elapidae family producing neuroparalysis. While cobra venom is post synaptic neurotoxin, the krait has pre synaptic neurotoxin. While the former produces local swelling and necrosis at the site of bite, the latter produces no local manifestation but may be painless. Both of them produce neuroparalysis like ptosis, external ophthalmoplegia, dysphagia as early features of systemic envenomation. They also produce flaccid quadriparesis, neck muscle weakness, respiratory paralysis which becomes fatal.

Russell’s viper and saw-scaled viper produce consumption coagulopathy due to presence of procoagulant enzymes resulting in incoagulable blood. Haemorrhage that is present in viperidae venom produce endothelial damage of blood vessels resulting in spontaneous bleeding. They also produce acute renal failure. Some of the Russell’s viper bite from south India has produced neuroparalysis with incoagulable blood. Neuroparalysis is due to presence of pre-synaptic neurotoxin. All viperidae bites produce local swelling due to presence of cytolytic or necrotic toxin.
Table 1: Medically important Species of Snakes in India excluding sea snakes

<table>
<thead>
<tr>
<th>Viperidae</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical vipers</td>
<td></td>
</tr>
<tr>
<td>• Daboia russelli - Russell's vipers</td>
<td></td>
</tr>
<tr>
<td>• Echis carinatus - saw-scaled or carpet vipers</td>
<td></td>
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<tr>
<td>• E sochureki</td>
<td></td>
</tr>
<tr>
<td>Pit vipers :</td>
<td></td>
</tr>
<tr>
<td>• Hypnale hypnale - hump-nosed viper</td>
<td></td>
</tr>
<tr>
<td>• Trimeresurus gram ineus - Indian bamboo pit viper</td>
<td></td>
</tr>
<tr>
<td>Elapidae</td>
<td></td>
</tr>
<tr>
<td>Cobra :</td>
<td></td>
</tr>
<tr>
<td>• Naja naja - common spectacle Indian cobra</td>
<td></td>
</tr>
<tr>
<td>• N kauithea - monocellate cobra</td>
<td></td>
</tr>
<tr>
<td>• N oxiana - North Indian cobra</td>
<td></td>
</tr>
<tr>
<td>• Ophiophagus hannah - King cobra</td>
<td></td>
</tr>
<tr>
<td>Kraits :</td>
<td></td>
</tr>
<tr>
<td>• Bungarus caeruleus - common krait</td>
<td></td>
</tr>
<tr>
<td>• B fasciatus - banded krait</td>
<td></td>
</tr>
<tr>
<td>• B sidanuus walli - Wall's sind krait</td>
<td></td>
</tr>
<tr>
<td>• B niger - black krait</td>
<td></td>
</tr>
</tbody>
</table>

Most common poisonous snakes of India

ANTI SNAKE VENOM (ASV):

ASV is the only definitive treatment of snake bite. It acts by neutralizing, circulating venom in the blood and tissue fluid. Anti venom is immunoglobulin usually enzyme refined F(ab)2 fragments of IgG purified from the serum or plasma of a horse or sheep that has been immunized with the venom of one or more species of snakes. Monovalent anti venom neutralizes the venom of one species of snake. Polyvalent anti venom neutralizes the venom of several different species of snakes. In India only polyvalent antisnake venom is available. There are several Indian ASV manufacturers (Table-II). In India antivenins are produced against 4 most important venomous snakes of India – Naja naja (cobra); B. caeruleus (Indian common krait); Russell's viper (Daboii Russelli) and saw-scaled viper (Echis carinatus). It is raised in horse serum. They are prepared in two forms – (1) lyophilized form which will be reconstituted with 10 ml water to 10 ml of ASV; (2) liquid form of ASV – each vial contains 10 ml of ASV. It should be preserved in +2° to 8° C. Each ml of polyvalent ASV produced in India neutralizes 0.6 mg dried Indian cobra venom, 0.45 mg dried common krait venom, 0.6 mg of dried Russell's and 0.45 mg dried Saw-scaled viper. Sometimes antibodies raised against the venom of one species may have cross reactivity against venom of closely related species which is known as paraspecific activity. ASV produced by Hoffkine Biopharmaceutical Company neutralizes venom of trimeresurus species due to paraspecific activity. Indian ASV contains F(ab)2 antibody and its half-life is approximately between 80-100 hrs.\(^3\)\(^12\)

WHEN TO USE ANTIVENOM:

The only action of antivenom is to neutralize circulating venom in blood and in tissue fluid. ASV is being prepared from horse serum and is associated with allergic reactions which may result in anaphylaxis and even death. It is costly and there is shortage of ASV in the world. Therefore, ASV should be used only when there is possibility of circulating venom in the body and not to all snake bite cases. Only 20% of bite resulting in significant envenoming needing ASV therapy.\(^4\) 50% of Russell's viper bite, 30% of bite by cobra, and 5-10% of bites by Saw-scaled viper do not result in any symptoms or signs of envenomation. Hence will not require ASV therapy.\(^5\) However, early administration of ASV is essential to neutralize the maximum circulating venom before it is fixed in tissue. Therefore, it should be given to cases with evidence of systemic envenomation as early as possible (Table-III). Patients with only local manifestations except two exceptions (Table-III) is not considered for ASV therapy as it may be present in non venomous snakebite cases and tight tourniquet. However, if the local swelling involve more than half of bitten limb and rapid extension of swelling beyond wrist or ankle within a few hours of bite are suggestive of venom driven swelling, needing ASV therapy. Development of enlarged tender lymph node draining the bitten limb is an early manifestation of poisonous snake bite needing ASV therapy. In case of viperidae snakebite (Russell's viper & Saw-scaled viper) causing haemostatic disturbance non-clotting of blood in 20 min whole blood clotting test (20WBCT) is useful bedside test for determining systemic envenomation. (Table IV) Evidence of spontaneous systemic bleeding such as gum and other internal bleeding indicates systemic envenomation needing ASV therapy.

In Elapidae bite (cobra & krait) and sometimes in viper bites in South India ptosis ophthalmoplegia are the initial manifestation of neuroparalysis needing ASV therapy. The primary indication of ASV administrations is abnormal 20WBCT.

The primary indication of ASV administration is incoagulable blood in 20WBCT or neurological deficit at the early period of snake bite.

Though ASV is most effective when administered early it may reverse systemic envenomic even when it has persisted for several days or in case of haemostatic abnormalities for two or more weeks.\(^2\) When there is no systemic envenomation the case should be observed for 24 hrs clinically and with repeated 20WBCT and then discharged.\(^2\)\(^3\)\(^4\)

SELECTION AND ADMINISTRATION OF ASV:

If the biting species of snake is known then the ideal ASV should
be monovalent ASV which is monospecific but identification of species of snakebite in India is difficult and only polyvalent ASV is available in India which acts against all four common poisonous snakes. Because there is great difference in snake venom even in a species of different geographical regions, ASV produced from the snake venom of the geographical area is the best ASV for the regions. Therefore polyvalent ASV produced in India should be used in snakebites in India.

It is administered by intravenous infusion diluted in approximately 5-10 ml/kg of body weight or 250-500 ml of normal saline or 5% dextrose in case of adults over a period of 1 hr to achieve the effective blood concentration rapidly. In intravenous push injection can be given but slowly (not more than 2 ml/min) which appears to be more cumbersome. Intra muscular injection of ASV is inferior in view of poor absorption. Local administration of antivenom at the site of bite is not recommended as it has not shown to be effective and extremely painful and may produce increase intra compartmental pressure.

### Table 3: Indications for Antisnake Venom (ASV)

ASV is recommended if and when a patient with proven or suspected snake develops one or more of the following signs:

- Early features of systemic envenoming
  - Haemostatic abnormalities
    - spontaneous systemic bleeding
    - non-coagulable blood in 20 min whole blood clotting test (20WBCT)
  - Neurotoxic signs
    - ptosis, external ophthalmoplegia dysphagia, paralysis
  - Cardiovascular abnormalities
    - Shock, cardiac arrhythmia
- Local envenoming
  - Local swelling involving more than half of the bitten limb (in the absence of a tourniquet).
  - Rapid extension of swelling (for example beyond the wrist or ankle within a few hours of bites on the hands or feet).
  - Development of an enlarged tender lymph node draining the bitten limb.

### Table 4: 20 minute whole blood clotting test (20WBCT)

- Place a few mls of freshly sampled venous blood in a small glass vessel.
- Leave undisturbed for 20 minutes at ambient temperature.
- Tip the vessel once.
- If the blood is still liquid (unclotted) and runs out, the patient has hypofibrinogenaemia ("incoagulable blood") as a result of venom-induced consumption coagulopathy.
- In India incoagulable blood is diagnostic of a viper bite and rules out a cobra bite.
- Warning: If the vessel used for the test is not made of ordinary glass, of it it has been used before and cleaned with detergent, its wall may not stimulate clotting of the blood sample in the usual way and test will be invalid.
- The vessel must the glass as it activate Hageman factor (FXII).

### Table 5: Comparison between venom yield per bite and neutralizing capacity of ASV

<table>
<thead>
<tr>
<th>Type of snake</th>
<th>Average yield of dry weight of Lyophilized venom per bite</th>
<th>Neutralizing capacity of 10 vials of ASV in India (100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naja naja (Cobra)</td>
<td>200 mg**</td>
<td>60 mg</td>
</tr>
<tr>
<td>B. caeruleus (Krait)</td>
<td>22 mg**</td>
<td>45 mg</td>
</tr>
<tr>
<td>Russell’s viper</td>
<td>150 mg** / 63 mg + 7 mg**</td>
<td>60 mg</td>
</tr>
<tr>
<td>Saw-scaled viper</td>
<td>4.6 mg**</td>
<td>45 mg</td>
</tr>
</tbody>
</table>

**Tun Pe, Toxicon 1986; 24 : 730. ** deoras PJ; 1965.

### Table 6: Effect of high (100 ml) and low dose (50 ml) of ASV as initial dose in viperine snakebite

<table>
<thead>
<tr>
<th>Parameters</th>
<th>High dose (n=40)</th>
<th>Low dose (n=40)</th>
<th>Comparison between Group-A &amp; Group-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of return of 20WBCT to normal</td>
<td>33.6 ± 1.36 hrs</td>
<td>42.32 ± 1.27 hrs</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>No. of Acute renal failure cases</td>
<td>5(12.5%)</td>
<td>15(37.5%)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>No. of cases undergoing haemodialysis</td>
<td>0</td>
<td>4(26.66%)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>No. of death</td>
<td>0</td>
<td>3(7.5%)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Total dose of ASV</td>
<td>1587 + 70 ml</td>
<td>1586 + 90 ml</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

**INITIAL DOSE OF ASV:**

There is great controversy regarding initial dose of ASV due to lack of study on venom level following snakebite and it’s changes with administration of various doses of ASV. Paul V et al. observed lower dose ASV as equally effective as high dose ASV. However, the initial dose should neutralize the most of the venom injected in the bite (Table V). In India long back (1965) Deoras PJ observed the venom yield/bite when milking the snakes once in a month. In another study, it is estimated that Russell’s viper yield 63 mg + 7 mg of venom/bite. WHO has recommended which has been accepted by others, that the initial dose of Indian polyvalent ASV is 100 ml. Thus it will neutralize 60 mg of Russell’s viper venom and cobra venom; 45 mg of krait and saw-scaled viper (Table V) which will be effective in neutralizing major amount of venom injected. In a recently concluded study we have observed that 100 ml ASV as initial dose has resulted in early return of 20WBCT to normal, less no. of acute renal failure, less no. of cases requiring haemodialysis and reduced mortality in comparison to 50 ml of ASV used as initial dose in viper bite (Table VI). Hence 10 vials of polyvalent ASV should be considered as initial dose of ASV in all type of snakebite in India.
DOES INTRA DERMAL SKIN TESTING IS INDICATED TO PREDICT ANTIVENOM REACTION PRIOR TO ADMINISTRATION OF ASV?

WHO has recommended that intra dermal skin testing should not be used before administering ASV. This test may reveal IgE mediated type 1 hyper sensitive reaction to horse protein but do not predict the large majority of early anaphylactic or late serum sickness type anti venom reactions as they are mediated by direct activation of complement system and not mediated by IgE. Skin testing only delay the administration of ASV and can in themselves be sensitizing. There are concerns raised by others for not doing intra dermal skin testing which needs further study.

ADVERSE REACTION TO ANTIVENOM AND ITS PREVENTION AND TREATMENT:

Usually more than 20% of cases will develop either early (within few hours) or late (5 days or more) allergic reactions following antivenom administration. Recently low incidence of early reaction to horse derived f(ab)2 antivenom has been observed in Thailand. In our cases only 4% develop early reaction. Early reactions are of two types – early anaphylactic reactions and pyrogenic reactions.

EARLY ANAPHYLACTIC REACTIONS:

It usually occurs in 10-180 min of starting antivenin. They develop urticaria, itching, cough, nausea, vomiting, abdominal colic, diarrhea, tachycardia. Majority of cases develop fatal anaphylaxis – hypertension, bronchospasm and angioneurotic oedema. In most cases they are due to direct activation of complement by IgG and residual FC fragment or direct stimulation of mass cells and basophils by antivenin protein. They are not type I IgE mediated hyper sensitivity reaction.

PYROGENIC REACTIONS:

It usually develop 1-2 hrs after starting ASV therapy. Fever, rigor, chill, lower blood pressure are the features. They are due to pyrogenic contamination of ASV and diluting fluid.

LATE SERUM SICKNESS TYPE REACTIONS:

It develops in 1-12 days after antivenin therapy (mean 7 days). Clinical features include fever, nausea, vomiting, arthralgia, arthritis, diarrhea, itching, recurrent urticaria, myalgia, lymphadenopathy, proteinuria, neuritis and even encephalopathy.

TREATMENT OF EARLY ANAPHYLACTIC AND PYROGENIC ANTIVENIN REACTION:

1. Switch off the antivenin administration.
2. Adrenaline 0.5 mg (1:1000 dilution) to be given intra muscularly for adult and 0.01 mg/kg for children. (Adrenaline 1 amp contains 1 mg in 1 ml). The dose can be repeated in 5-10 min if the patient’s condition deteriorates. It is the drug of choice.
3. Chlorpheniramine maleate (adult 10 mg) given intravenously over few minutes.
4. Hydrocortisone (adult 100 mg) intravenously. The corticosteroid is unlikely to act for several hours, but may prevent recurrent anaphylaxis.
5. Ranitidine – adult 50 mg given slow IV.

TREATMENT OF PYROGENIC REACTION:

1. Oral paracetamol and physical cooling to reduce temperature.
2. Intravenous fluid to correct hypovolaemia.

TREATMENT OF LATE REACTION TO ASV:

They usually respond to oral antihistamine. Patients who fail to respond in 24-48 hrs should be given a 5-day course of prednisolone (5 mg hourly for 5-7 days in adult).

PROPHYLAXIS AGAINST ALLERGIC REACTION TO ASV:

In a recent cochrane review, it has been concluded that prophylactic adrenaline 0.25 mg given subcutaneously has shown fewer allergic reactions but not with prophylactic antihistaminics. There is no trial on prophylactic corticosteroids Prophylactic adrenaline in all cases raises concern about the safety. WHO has not recommended routine use of prophylactic drug to prevent ASV induced reaction. But cases with high risk of reaction to ASV (patient with history of atopi and reaction to equine antiserum) should receive subcutaneous adrenaline, intravenous antihistaminic intravenous Ranitidine and corticosteroid.

CONTRAINDICATION TO ASV:

There is no absolute contra indication to ASV treatment but patient were atopic (like severe asthma) and/or who have reacted to horse serum in the past should be given ASV only if they have signs of systemic envenoming after giving prophylactic adrenaline subcutaneously.

TIMING AND DOSE OF REPEAT OF ANTIVENOM ADMINISTRATION:

In vipers snakebite who develops haemostatic abnormality and received initial dose of ASV a gap of 6 hrs is needed to restore clotting factors by the liver. Non-clotting of blood in 20WBCT after 6 hrs of initial ASV therapy is the indication of administering the repeat dose of ASV of same amount (100 ml). 20WBCT should be carried out every 6 hourly to determine
the further dosing of ASV till the test become normal. Then 20WBCT should be repeated 12 hourly for 48 hrs to determine any reversal of coagulation abnormality. Spontaneous systemic bleeding like gum bleeding usually stops within 15-30 minutes of ASV administration. In patients who continue to bleed briskly, the dose of anti venom should be repeated 1-2 hrs after the first dose of ASV (Table VII). 200 ml of polyvalent ASV is usually adequate to restore the coagulation abnormality in viperidae bite. 

In Elapidae with improvement in neuroparalysis is seen after 30 minutes of ASV administration. Considering the rapid deterioration in Elapidae bite resulting in respiratory paralysis which is not reversible with ASV after the venom is fixed on the tissue; a repeat dose of 100 ml of ASV is needed after 1 hr of observation after first dose of ASV if there is no improvement or deterioration in neuroparalysis (2,12) (Table VII). If there is no improvement after 200 ml of ASV further dose of ASV may not able to reverse respiratory paralysis and the cases should be kept in I.C.U. for consideration of artificial ventilation when the need arise. This need further study.

RECUURRENCE OF SYSTEMIC ENVENOMING:

Recurrency systemic envenomation has been observed within 24 to 48 hrs of initial recovery. It is due to continuing absorption of venom from the deposit at the site of bite, perhaps after improvement in blood supply following correction of shock and hypovolemia and disappearance of ASV from circulations. It is seen less in India in view of prolonged half-life of polyvalent ASV produced in India (80-100 hrs). The recurrence may also be due to redistribution of snake venom from tissue into vascular space as a result of antivenin therapy.

Hence cases of snake bite should be observed for 48 hrs after recovery.

CONCLUSION:

Lack of research in snakebite prevent the development of evidence based therapy of antivenom venom use in snakebite. However, the present WHO guidelines for South-East Asia and subsequent consensus statement from India is the right essential step to rationalize antivenom venom therapy which is most effective and to promote further research in the subject in India.

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**REFERENCES:**

10. Deoras Pj. 1965. Snake in India; National Book Trust India; P33.