Use of Anti-snake venom in India – Practical Issues
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Introduction
Is Indian anti-snake venom an optimal antidote?
Snake bites result in about 50,000 deaths per year and anti-snake venom (ASV) is the cornerstone of management of snake-bite envenomation. Anti-snake venom was discovered in 1896 by Dr. A. Calmette. It contains immunoglobulins (enzyme refined fragments of IgG) obtained by collecting serum or plasma from horses or sheep that have been immunized with the venom of different snake species. This was the technique that Dr. Calmette used for preparation of ASV, and is still being followed today with some changes in processing and purification.

In India there are certain issues that need to be addressed with respect to anti-snake venom. The issues concern variations in efficacy, cost, allergic reactions and dosing which make it a less than optimal antidote in a case of snake bite envenomation. The aim of this review is to discuss these issues and the possible ways to address some of the problems inherent in using the ASV preparation available in India.

Variability in the efficacy of ASV
The ASV available in India is a polyvalent ASV that has efficacy against the venom of 4 snake species also known as the ‘big four’ (Indian cobra, krait, saw-scaled viper and Russel’s viper). However, there appears to be variability in the efficacy of ASV across the different snake species and even within the same species. In a study done in Vellore (CMC and Government Medical College, Vellore), ASV was found to be more effective in Saw Scaled Viper and Indian Cobra bites (unpublished data). ASV was relatively less effective in Russel’s Viper bite (increased death rate, transfusion and dialysis) and Common Krait bite (increased death rate and mechanical ventilation).

In our experience we also found a batch to batch variability in the efficacy of ASV. There was an increase in the death rate, in our experience when that certain batch of ASV was used. This was resolved when a particular batch of ASV was discontinued and a new batch was used. Subsequent ELISA analysis of these batches showed that the titre of specific antibodies varies between different batches of ASV, and titres were low in the batches associated with a higher mortality. (unpublished data).

Reasons for variability of efficacy of ASV
There are many reasons for the observed variability of ASV efficacy and these are related to the source, method of production and action of the antivenom.
1. **Source:** About 85% of venom extracted for antivenom production comes from one source – The Irula Co-operative Society near Mamallapuram, Tamilnadu. It is known that venom composition varies even within the same species in different parts of the country. Therefore ASV produced from one source may show geographical variability and not have the same efficacy all over the country.

2. **Production of ASV**
   There are quality control issues related to venom extraction and production. The quality of venom varies according to the age of the snake and season. Also, if the venom is not frozen immediately, there may be inactivation of the enzymes within.
   
   After extraction, the venom is sent to pharmaceutical companies. Here, the venom is injected into horses and blood is then collected periodically from the immunized animals. Serum is extracted from the blood, antibodies are precipitated, then purified using an enzyme digestion method and finally sterilized before the final product is made available either in a liquid or lyophilized form. Variability in any of the steps in production can result in variability in efficacy. The immune response to venom in the horse varies from individual to individual. Quality control issues in the final purification and production of ASV also influence the efficacy of the product.

3. **Low title of neutralizing antibody**
   Studies show that the bulk of antibodies in anti-snake venom are not against snake proteins. This means that the purification procedures are unable to separate specific antibodies against venom proteins and non-specific antibodies. Only 20% of ASV has specific antibodies against venom protein. Of these only 5% antibodies have capacity to specifically neutralize the toxic effect of venom proteins (venom-neutralising antibody). This essentially is the problem with Indian polyvalent antiserum.

4. **Complexity of venom**
   The venom from any species is complex and may comprises of around 25 enzymes and polypeptides which vary from snake to snake. Many of the toxic venom proteins are of low molecular weight and many not be immunogenic. Therefore ASV produced may not contain antibodies against all the individual toxic venom proteins. Venom protein variability within a species only compounds this problem. Therefore it is not clear that each venom sample that is used for horse immunization has similar composition. Therefore the resultant ASV that is purified, may vary in its antibody composition.

5. **Tissue bound venom proteins**
   Krait venom travels to the neuro-synaptic junction and binds with the pre-synaptic terminal. The ASV given does not neutralize tissue bound venom protein and is therefore relatively ineffective in Krait bite envenomation. This may true of Russell’s viper envenomation where muscle injury and kidney injury have set in even before the patient presents to the hospital and cannot be effectively neutralized by ASV. Although ASV may bind circulating venom proteins, it cannot reverse the action of tissue bound proteins and their consequences.

6. **Inter species and intra species variability**
   The polyvalent ASV produced in India is specifically made to neutralize venom from four species (known as the ‘big four’ – Indian Cobra, Common Krait, Russel’s Viper and Saw Scaled Viper). The ASV may be ineffective against other species of snakes which are known to bite humans even if they belong to the Elapidae or Viperidae families. Antibodies against the venom of one species is sometimes known to have a cross...
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reactivity against venom of a closely related species.

The need for improved antivenom

The figure given below is a timeline demonstrating the evolution of ASV over the years. Despite improvements in purification, stability and efficacy, the basic method of production of ASV however has not changed over the last 120 years (antibodies are still derived from serum of immunized horses). As a result ASV continues to be associated with a very high rate of anaphylactic reaction. This, along with geographic variations in the venom constituents and variability in efficacy due to quality control issues makes ASV a less than optimal antidote for management of snake bite envenomation in India.

Some suggestions for an improved antivenom are as follows.

1. **Venom from different geographical sources:** This will improve the efficacy of ASV across India as antibodies will be developed against a greater variety of venom proteins.

2. **Identification of the specific neutralising antibodies** for venom proteins: This may result in a more efficient ASV and with a lower rate of anaphylaxis.

3. **Improvements in the production process**

4. **Tests to assess quality of ASV**

5. **Monoclonal technology** to develop a cocktail antivenom

References


2. Simpson ID. A study of the current knowledge base in treating snakebite amongst doctors in the high risk communities of India and Pakistan : does snakebite treatment training reflect local requirement? Trans Royal Society of Tropical Med and Hygiene 2008; 102 : 1108-1114


