ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Pattern of Use and Adverse Reactions to Antisnake Venom in Haemotoxic Snake Bite

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ABSTRACT

Snake bite is one of the major public health problems in India. Antisnake venom is the mile stone and the only mainstay therapy in the management of snake bite. In India polyvalent Antisnake venom is used. Antisnake venom is a double edged sword. It has got risks of anaphylactic reactions. It is also a scarce and costly commodity.It should be used cautiously with regard to its dose, cost, and adverse rections.So this study was done to evaluate the pattern of use and adverse reactions to Antisnake venom in haemotoxic snake bite in a tertiary care hospital. Institutional ethical committee clearance was obtained.About 212 snakebite vicims with haemotoxic envenomation were studied from the time of reporting to the hospital and followed up till their discharge.About 59.9% developed early adverse reactions. Itching and urticaria (40.94%) was most common followed by nausea,vomiting and abdominal pain(18.11%). The time of onset of reactions were between 5 and 60 minutes. The adverse reactions were simple to manage with available drugs. No death occurred due to acute anaphylactic reaction.Prophylaxis with Adrenaline significantly ($p<0.05$) reduced the incidence of reactions. The complications due to snake bite was minimum if Anti snake venom was administered within first 8 hours.

Keywords: Anti snake venom, Haemotoxic envenomation, adverse reactions, Adrenaline

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ISSN: 0975-8585

INTRODUCTION

Snake bite is one of the major public health problems in the tropics. It is also emerging as an occupational disease of agricultural workers. In view of their strong beliefs and many associated myths, people resort to magico –religious treatment for snake bite thus, causing delay in seeking proper treatment. Many deaths occur before they reach the hospital. India alone contributes to 81,000 envenomations and 11,000 deaths annually[1].

Antisnake venom (ASV) is the mile stone in the management of snake bite. Antivenom is immunoglobulin derived from the plasma of a horse, donkey (equine) or sheep (ovine) that is immunized with the venoms of one or more species of snake[2] In India polyvalent ASV is used. They are effective against all the four common species; Russells Viper *(Daboia Russeli),* Common Cobra *(Naja Naja),* Common Krait (*Bungarus caeruleus)* and Saw scaled Viper (*Echis Carinatus).* Haemotoxic envenomation is produced by viper bite. Viper bites are often, but not always are characterized by severe pain, quick onset(within a couple of hours) of local swelling spreading rapidly across the nearest joint and tender regional lymphadenopathy. Occasionally severe Russels viper systemic envenoming may develop in the absence of a local reaction. Bleeding from fang marks,blistering and necrosis are well established within 24 hours. Bleeding abnormalities dominate the clinical picture of these patients. Haemorrhagins in venom produce wide spread bleeding which may be obvious from gums,nose,GI tract, kidneys and urinary bladder. Sometimes bleeding in tissue planes leads to large haematoma. Consequent to bleeding, hypovolemia and shock may superveneViper bites contribute substantially to the burden of acute renal failure. While recovery from acute tubular necrosis can be complete ,some patients develop cortical necrosis with varying degrees of renal insufficiency after recovery from acute event. Some develop end stage renal disease.[3] At present there are no monovalent Anti snake venoms. This is because there are no definitive means of identifying the snake species, in the absence of the dead snake. Kit for detection of snake venom and venom antibody are not available in India [4].

All patients receiving ASV are at risk of adverse reactions as they contain foreign proteins]. The risk of reactions is dose-related, except in rare cases in which there has been sensitization (IgE-mediated Type I hypersensitivity) by previous exposure to animal serum, for example, to equine antivenom, tetanus-immune globulin or rabies-immune globulin [5].

Early reactions occurs 10-60 minutes after starting IV antivenom Cough, tachycardia, itching (especially scalp), urticaria, fever, palpitations, nausea, vomiting, headache can occur. Over 5% with early reactions develop manifestations of severe systemic anaphylaxis: hypotension, bronchospasm, angioedema .Most of the fatal reactions are not reported as they are falsely related to snake venom rather than ASV. These are not acute hypersensitivity reactions mediated by IgE antibodies against animal proteins .This is because IgE antibodies are not detected by skin testing or radioallergosorbent tests (RAST). Activation of complement system by IgG aggregates or residual Fc fragments or direct stimulation of mast cells or basophils by antivenom protein are more likely mechanisms for these reactions.

Pyrogenic reaction develops 1to2hours after treatment Chills, cutaneous vaso constriction goose flesh, shivering, drop in temperature, sweating, vomiting and diarrhea can occur. Children may develop febrile seizures. These reactions are due to contamination of ASV with pyrogens during manufacturing process. These reactions are commonly reported.

Late(serum sickness) type reaction develops 1-12 (mean7) days after treatment. Clinical features include fever,nausea, vomiting, diarrhoea, itching, recurrent urticaria, arthralgia, myalgia, lymph adenopathy, periarticular swellings, mononeuritis multiplex, proteinuria, with immune complex nephritis and, rarely encephalopathy. It is a type III Hypersensitivity reactionWhen patients with early reactions are treated with steroids and antihistamines the chance of developing late reactions are minimal [6].

.Incidence of early adverse reactions varies between 5-80%.The deaths due to ASV reactions are falsely attributed to envenomation. As early reactions are common, unpredictable, and occasionally life threatening, all patients treated with antivenom must be regarded as potentially reactive [7]. As a result prophylactic treatments including combinations of adrenaline, antihistamines and/or corticosteroids have been used concurrently with antivenom since the 1960's. However, in the last decade, studies of the efficacy and safety of premedication strategies have been conducted in Sri Lanka and Brazil. It shows that premedication with subcutaneous adrenaline produced a significant reduction in the incidence of early adverse reactions. But antihistamine and hydrocortisone appears to be of no obvious benefit in preventing acute reactions due to antisnake venom. Adverse reactions to antisnake venom cannot be predicted by test dose. Since the majority of early (anaphylactic) or late (serum sickness type) antivenom reactions result from direct complement activation rather than from IgE mediated hypersensitivity, these tests are not predictive. They may delay treatment and can in themselves be sensitizing. So these tests should be avoided . Anti snake venom remain the only mainstay therapy for snake bite. In the management of a snake-bite victim the physician should first decide whether or not to administer antivenom.[2] .ASV is a scarce and costly commodity. It should be administered only when there are definite signs of envenomation. The venom which is free and unbound in the blood stream or tissue fluid can only be neutralized. In India there is considerable irrationality in the usage of ASV. This is probably due to fear, inadequate experience and improper training [8].

Antisnake venom should not be withheld due to danger of reactions in indicated patients as complications due to snake bite appeared to be a far greater risk than adverse reactions to anti snake venom. Even if patients develop anaphylaxis there is no other alternative other than Antisnake venom.Appropriate guidelines should be followed for its administration.

ASV should be used cautiously with regard to its dose,cost, and adverse rections.So this study was done to evaluate the pattern of use and adverse reactions to Anti snake venom in a tertiary hospital.

ISSN: 0975-8585

MATERIALS AND METHODS

The present study was carried out in haemotoxic snake bite victims admitted in Department of Medicine and Institute of Paediatrics, Government Rajaji Hospital,Madurai,for a period of twelve months after obtaining Institutional Ethical Committee clearance.It is a prospective observational study.Inclusion criteria includes.patients with evidence of haemotoxic envenomation such as, spontaneous systemic bleeding from gums(epistaxis) and coagulopathy (non coagulable blood in20 min whole blood clotting test- 20 WBCT,thrombocytopenia) . Exclusion criteria includes snake bite victims without definitive signs of envenomation ,persons previously sensitized with antisera(tetanus or diphtheria), allergic/atopic individuals and those who were treated with ASV elsewhere,prior to admission. Written informed consent was obtained .All snake bite victims with evidence of haemotoxic envenomation were studied from the time of reporting to the hospital and followed up till their discharge. Premedications like Pheniramine maleate 0.5mg/kg and Dexamethasone 0.1-0.4mg/Kg were given to all patients five minutes prior to administration of ASV. In some patients Adrenaline 0.25mg of 1in 1000 was also given subcutaneously. The Antisnake venom was given as an intravenous infusion in 100 ml of normal saline at 10-15 drops per minute. The initial dose is 10 vials.The vital signs were monitored at 5 minutes interval for first 30 minutes and then at 15 minutes interval for two hours. If the patient did not develop any adverse reactions the ASV was administered in one hour. The recording of one or more of the following features, soon after start of antivenom administration, was considered indicative of an adverse reaction. It includes non eruptive itching, urticarial eruption, dry cough, wheeze/bronchospasm, head ache ,nausea/vomiting, abdominal pain, stridor, angioedema of lips and mucous membrane hypotension(Systolic BP ≤80 mm of Hg,and/Diastolic BP≤ 50 mm of Hg), tachycardia(≥100bpm), low volume pulse, central cyanosis, febrile convulsions,pyrexia(Temperature≥39 degree Celsius) rigor, Sweating and cold clammy skin.Following an adverse reaction ASV was discontinued. Inj Adrenaline 0.1 ml of 1 in 1000 was given subcutaneously. In addition Hydrocortisone 2-6 mg/Kg iv and Inj Pheniramine 0.5 mg/Kg iv was also given. Once the patients had recovered, ASV was restarted slowly keeping the patient under close observation. Clotting test was performed six hours after initial dose. If it is prolonged repeat dose of ASV was given. If the total dose was more than 24 vials FFP(Fresh frozen plasma) was given

The following datas like age, sex, occupation,nature of snake,time of snake bite,anatomical site of bite,time interval between snake bite and ASV administration, total quantity of ASV given and laboratory investigations were collected from patient history, perusal of case sheets and the attending physician. The data was entered in Microsoft excel spread sheet and analysed by simple descriptive statistics. The association between variables were assessed by Chi-square test.

RESULTS

During the study period about 212 snake bite victims with evidence of haemotoxic envenomation were analysed. The following observations were made

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The age of the victims ranged from 8-65 years. The mean age was 32.15 years(SD±12.45),median was 34 years. Of the 212 cases seen there were 168 males and 44 females. Both males and females were predominant between the age group 30 and 39.

A total of 2653 vials of ASV were used in making a mean usage of 12 .5vials. 10 vials was the initial dose.Repeat dose of ASV was given in 40.56 % of patients.Fresh frozen plasma was given in 26 patients. All the 212 snake bite victims received ASV. Adverse reactions occurred in 127(59.9%) of patients.Itching and urticaria were the most common presentation(40.94%),followed by nausea, vomiting & abdominal pain (18.11%). The incidence of pyrogenic reactions were 12.59%.(Table-1)The time of onset of reactions were between 5 and 60 minutes.The average time was 18 minutes. Prophylactic drugs like pheniramine maleate and dexamethasone were given to all patients receiving ASV .Adrenaline was given to 18 patients along with above drugs.Addition of adrenaline significantly reduced the incidence of adverse reactions.($P<0.05$).(Table-2) About 25 patients developed acute renal failure. There was one death due to pulmonary edema and all the other patients recovered with dialysis.One patient developed cellulitis.The time interval between snake bite and ASV administration was less than 8 hours in 88 patients and more than 8 hours in 124 patients.The mean time was 10.42 hours,(SD±8.61 hours). When the time interval between snake bite and ASV administration was more than 8 hrs the incidence of complications were significantly high. ($p<0.05$).(Table-3) Antibiotics such as Cephalosporins and metronidazole were used to treat secondary infections.

Table 1: Type of Adverse Reactions to ASV

Reactions	Total	Percentage
Itching,urticaria	52	40,94
Nausea,vomiting,abdominal pain	23	18.11
Fever,rigor	16	12.59
Cough,bronchospasm	13	10.23
Hypotension,tachycardia	12	9.44
Sweating,cold clammy skin	7	5.51
Head ache	4	3.14

ISSN: 0975-8585

Table 2: Effect of Prophylactic Drugs on Adverse Reactions to ASV

Drug	Reaction	No reaction	Total
Pheniraminemaleate+Dexamethasone	124	70	194
Pheniraminemaleate+Dexamethasone +Adrenaline	3	15	18

Table 3: Correlation between Bite to Needle Time and Complications

Bite time to needle time	Complications	No complications	Total
< 8 hrs	1	87	88
>8 hrs	25	99	124

DISCUSSION

Snake bite is a significant health hazard that leads to high mortality rate especially in India.[9] It is a medical emergency. The only available antidote is Anti snake venom. In India Polyvalent ASV is used. Monovalent ASV is not used as there are no specific means to identify the snake or detect the venom. As the therapy is administered based on clinical features and with the victims developing more than one features, the use of polyvalent ASV in India is justified.

Although Antisnake venom is costly it should not be withheld for fear of reactions as the management of snake bite without ASV is even costlier. The present study analyses the pattern of use and adverse reactions to Antisnake venom.

In this study 62.3% of snake bite victims were in 20-39 years age group. Thus it shows that snake bites occur especially among active workers .The bites were common during night and in the lower limb. The incidence of snake bite and anaphylactic reactions were common in males and this might be due to the fact that males travel more at night rather than females [10].

In this study ASV was given to 212 snake bite victim according to guidelines given by World Health Organization[2]. Studies have shown that test doses do not predict adverse reactions to anti venom as they are not mediated by Ig E antibodies but by activation of complement. They may also pre-sensitise the patients. So skin testing was not done. Trials conducted in Srilanka have shown that prophylactic drugs are ineffective in preventing adverse reactions to ASV. In this study prophylactic drugs like, antihistamines and corticosteroids were given to all the patients receiving ASV. For some patients adrenaline was also given as they aim

for maximum safety for the patients, inspite of the absence of definitive trial evidence. But addition of adrenaline significantly reduced the adverse reactions.

The initial dose of ASV should neutralize the average amount of venom injected. In this study 10 vials of ASV was the initial dose. The result shows that adequate initial amount was used which is in accordance with National Snake Bite Treatment Protocol 2007[11].

In patients with Haemotoxic envenomation,clotting test was performed six hours after initial dose. If it is prolonged repeat dose of ASV was given. This is because the liver cannot replace clotting factors within six hours. Clotting tests and repeat doses of ASV was continued on a 6 hourly pattern until coagulation was restored. The maximum amount of ASV that was used for haemotoxic envenomation was 24 vials .As one vial neutralizes 6 mg ,this would have neutralised 144 mg of venom .The range of venom injected is 5mg-147 mg. This is sufficient to inactivate unbound venom. Therefore further administration of ASV is of no use. In this study Fresh Frozen Plasma was used when more than 24 vials were used and the coagulation abnormality was also corrected. More clinical trials are warranted in these areas.

In the present study 12.26% of the patients developed complications due to snake bite. An attempt was made to find the relationship between the development of complications and the time interval between snake bite and administration of ASV. It was found to be significant ($p<0.05$). This finding is similar to the observation made in Srilanka that the occurrence of complications especially renal failure was directly related to the duration of venom in the vascular space prior to inactivation by ASV.

In this study 59.9% of patients who had received antisnake venom were affected by adverse reactions. This is similar to study in Sri Lanka where 55.4% of patients developed adverse reactions[12]. All the reactions occurred with initial dose .The most common presentation of anaphylactic reactions was urticaria(45.97%).The investigations carried out in Srilanka also registered urticaria as a common presentation. This is due to release of histamine from mast cells. The incidence of pyrogenic reactions was 12.59%.However this is less when compared to study in Kerala where pyrogenic reactions accounted for majority. These reactions are due to pyrogen contamination of ASV during manufacturing processes. Good manufacturing practices should be followed to prevent this. The time interval between the ASV initial dose and the onset of symptoms differed in the study. The earliest response was recorded 10 minutes after ASV administration while the delayed one occurred 60 minutes later. The average interval observed was18 minutes. This shows that patients receiving Anti Snake venom should be closely monitored for 1-2 hrs.

Tetanus toxoid was administered to all the patients .Antiboitics are not routinely indicated but whenever the patients were bought with incised bite wound, antibiotics was given to prevent the secondary bacterial infections [13].

The study suggests that Antisnake venom was a effective antidote and its use is justifiable whenever indicated without alarm. The adverse reactions were simple to manage

with available drugs. No death occurred due to acute anaphylactic reaction.These reactions are not an indication to withhold or stop ASV. One has to give ASV under cover. The complications due to snake bite was minimum if bite to needle time was less than 8 hours.

CONCLUSION

This study was conducted to analyse the pattern of use and adverse reactions to antisnake venom. The main findings of the study are as follows. The incidence of snake bite and adverse reactions were common in males .There was no fixed dose as the individualized doses were titrated according to patients symptoms. The average vials of ASV that reversed the effects of haemotoxioc envenomation was 12.39. Complications like cellulitis,and acute renal failure were high when the bite to needle time was more than 8 hours. The incidence of adverse reactions to Antisnake venom were 59.9%.Urticaria was the most common presentations(40.94%) followed by nausea vomiting & abdominal pain(18.11%). There was no death due to acute anaphylactic reactions. All the reactions occurred with initial dose and did not recur with repeat doses. The reactions were treated with antihistamines, adrenaline and corticosteroids. Prophylactic drugs like Pheniramine maleate and dexamethasone were not effective. But when Adrenaline was added it reduced the rate of adverse reaction

Anti Snake venom available for use has escaped the mandatory stringent clinical trials. ASV reactions are more linked to the manufacturers than the chemical aspects of venom .Further researches are required to obtain pure and cheap Anti snake venom by following good manufacturing practices. In the future antivenoms may be replaced by humanized antibodies, specific neutralizing compounds or vaccination [14].

We should shift our focus towards development of monovalent ASV as they are more effective and less costly with a significantly better side effect profile. Micro-Elisa Kit for detection of snake venom should also be developedCommunity education is also important so that following a snake bite they seek proper treatment as quickly as possible. Early administration of ASV prevents morbidity and mortality [15].

In the future we can aim at obtaining the venom by recombinant DNA technology so as to prevent unnecessary sometimes life threatening adverse reactions due to Anti snake venom. To conclude Antisnake venom is a life saving weapon. It should be administered to indicated patients and should not be with held for fear of reactions.The reactions are easily managed. So careful usage of ASV with special concerns on cost, dose and side effects are essential in the routine mangement.

ACKNOWLEDGEMENT

The authors would like to acknowledge the department of Medicine and Institute of Paediatrics ,Government Rajaji Hospital ,Madurai,for their kind co operation and valuable inputs.

ISSN: 0975-8585

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