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Original Research Article

Anti-snake venom induced reactions among children with snake envenomation

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ABSTRACT

Background: Snake envenomation in children is a neglected tropical condition with high morbidity and mortality. Life threatening neurotoxic and hemotoxic envenomation in children demands timely Anti Snake Venom (ASV) administration to improve the outcome.
Methods: This was a prospective observational study undertaken at the pediatric intensive care unit of tertiary care referral center at Chengalpattu. All the 26 children with evidence of snake envenomation were recruited after informed consent of the caregivers during the study period. Clinical presentation and ASV related reactions were studied.
Results: In this study of 26 children with envenomation, neurotoxic envenomation was more common. Foot was the common bite site. 10 of the 18 children (55.5%) had nocturnal bites. Ptosis, local swelling, hypotonia, headlag, vomiting and shock were the common clinical features. Polyvalent antivenom was used in all these children. ASV reactions of varying severity was encountered in 18 of the 26 children (69.2%). All the acute ASV reactions were encountered in the first 30 minutes. All the 18 children had rashes to begin with. Rashes and itching were the common feature of ASV reactions. Among children with reactions shock was seen in 50 %. Overall mortality was 3.85% (one child). None died due to anaphylaxis. The administration of ASV in primary and secondary centers was not carried out in time and the occurrence of anaphylaxis were not managed with inj adrenaline prior to referral. Inj pheniramine maleate, atropine and hydrocortisone were used by those centers. Referral after ASV reactions led to delay in completion of ASV administration.
Conclusions: Occurence of ASV reactions is high in children (69%). There is an undue delay in ASV completion with ASV reactions. There is an urgent need for prevention of ASV reactions either by monovalent venoms or premedication prior to ASV administration.

Keywords: Anti-snake venom, Anaphylaxis, Reactions, Snake envenomation

INTRODUCTION

Snake envenomation is still a major problem encountered in children from rural areas. Globally, between 1.2 million and 5.5 million snakebites occur annually leading to as high as 1,84,1000 envenomings and 94,000 deaths.[1] Snake envenomation is a neglected tropical disease and is a disease of poverty. Snake envenomation in pediatrics is associated with increased morbidity and mortality. The reported mortality varies from 1.8% to 13.3%.[2-4] Polyvalent anti snake venom (ASV) is the only available specific antidote. Children sleeping outdoors or lying in the floor indoors are at an increased risk of snake bites. In the absence of specific tests other than 20-minute whole blood clotting time, to suggest snake envenomation pediatricians are forced to start anti snake venom in

children based on the course of events and clinical features of envenomation in the absence of history of bites especially with nocturnal krait bites. Associated reactions to ASV in such situations is a nightmare for the treating physician despite counseling the parents. The reactions vary in severity from mild rashes to severe anaphylaxis induced hypotension and respiratory failure. Based on the existing literature very few data are available with regard to the anti-snake venom induced reactions in children. This study was undertaken to evaluate presentation and the reactions associated with ASV administration in children less than 12 years of age.

The objective of this study was to identify the clinical presentation of snake envenomation and evaluate the ASV reactions among children at a pediatric tertiary care center. Prospective observational study. This was done at the pediatric intensive care unit (PICU) Chengalpattu Medical College, a semi urban pediatric tertiary care Institute, in the government sector. Duration: January 2015 to May 2016. All children with evidence of snake envenomation with or without history of snake bite were recruited for the study. Exclusion criteria: ChiIdren with snake bite who were treated elsewhere and whose treatment details were not available or traceble as per the data collection proforma were excluded. Sample size: All children with snake envenomation who satisfied the inclusion exclusion criteria during the study period were recruited for the study.

METHODS

Children were recruited for the study after informed consent from the parents or care givers. Study parameters include a detailed history, clinical examination for signs of neurotoxic, hemotoxic and or local envenomation, chronology of events leading to hospitalization, site and setting of bite, type of snake, bleeding either from the bite site or from any other site, swelling at the site of bite, ptosis, respiratory difficulty, neuroparalysis, head lag, hypotonia, dysphagia, diplopia, drooling of saliva, dysgeusia, altered sensorium, vital signs on admission, pupillary size, pupillary reaction, extra ocular movements, hypotonia, absent reflexes, prehospital therapy, time interval from bite to hospital admission, time interval from bite to administration of ASV, occurrence of ASV reactions, nature of reaction and dose of ASV given. Following were the definitions used to categorize reactions to ASV. Early anaphylactic reactions occur within the first 60 minutes of starting ASV. Indications for ASV administration included presence of signs of neurotoxic envenomation (Ptosis, dysphagia, perioral numbness, diplopia, weakness, paralysis and areflexia), hemotoxic envenomation (persistent oozing of blood from the bite site, prolonged 20minute whole blood clotting test.) and local envenomation (swelling crossing a major joint close to the bite site or increasing swelling during hospital stay, any swelling that is more than half the limb bearing the bite site. The care givers were explained the risk of envenomation and the need of ASV and the reactions associated with administration. ASV was administered without any test dose. Initial dose was 10 vials and subsequent 10 vials as per unit policy for persistent signs of envenomation. Children were closely monitored for anaphylaxis. The following definitions were used for the study. Mild anaphylactic reactions were rashes, nausea, vomiting, diarrhoea, headache, itching and fever. Severe reactions were bronchospasm, hypotension and angioedema. Pyrogenic reactions - fever, chills, vasodilatation, hypotension and seizures. These are the reactions were those encountered between 1-2 hours of ASV. With any sign of anaphylaxis the ASV infusion was stopped. Anaphylaxis was treated as per standard protocols. After stabilization ASV was restarted. If the child developed further reaction it was treated similarly and ASV was restarted. Despite the treatment if child continued to develop anaphylaxis ASV was continued after intubation, mechanical ventilation and inj adrenalin infusion. 20-minute whole blood clotting test at admission and repeated as per protocol, complete blood count, electrolytes, urea creatinine, peripheral smear study were undertaken. Urine output was monitored as also the progression of swelling at the bite site, bleeding, discoloration, ulceration and features of compartmental syndrome. Children with swelling at the site of bite progressing to discoloration and ulceration were treated by pediatric surgeon and plastic surgeon as indicated. All children were followed up till discharge or death in case of mortality. Children discharged home were advised to return for follow up if they encountered any of the following signs and symptoms for serum sickness in the next 4 weeks. Pruritus, urticaria, arthralgia, lymphadenopathy, peri articular swelling, and neurological impairment including encephalopathy. Data was analysed using Epi Info statistical software. Descriptive statistics was used to express results about ASV use, early adverse reactions to ASV, time of occurrence and its recovery and clinical outcomes. Proportions and percentages were obtained. Study was undertaken after Institutional ethical approval.

RESULTS

27 children were admitted with history of snake bite during the study period, of whom 23 had features of envenomation and were treated with ASV. 2 Children, without envenomation and 2 children who received ASV elsewhere were not included. 3 children were treated with ASV based on the clinical presentation without history of snake bite. Overall 26 children admitted with features of snake envenomation, received ASV. Gender distribution revealed 8 female children and 18 male children. Male female ratio was 2.25: 1. Thirteen children were less than 5 years (50%), 11 were between 6-10 years (42%) and 2 were more than 10 years. The site of bite was predominantly in the foot (n-18 -69.2%) followed by hand (n-5), not known in 3. The setting of bite was indoor in 10 (42%), outdoor in 10 and unknown in 6. Majority of them were not able to identify the type of snake. The time of bite was between 7pm to 7 am in 10(42%), 7am to

1pm in 9 and 1-7pm in 5 children. Poor visibility in case of nocturnal bite was encountered in 10 of the 26 snake bites. Among the 26 children, two third of the study group were referred and 1/3 rd attended the hospital on their own. Among the children referred to our Institute 6 were mechanically ventilated. Native treatment in the form of oral medication and local application was encountered in 4 children. Among the 26 children 20 (77%) had neurotoxic envenomation, 4 (15.4%) had only local envenomation, 2 had hemotoxic envenomation. A combination of hemotoxic envenomation and local cellulites was encountered in one child and neurotoxic envenomation with local cellulites was encountered in 14 children. The clinical features of children at admission is summarized in Table 1. 6 children presented with shock at admission. Fluid boluses in these children varied from 20 ml/kg to 100 ml/kg. The time interval between bite and commencement of ASV ranged from 30 minutes to 9 hours with a mean of 3.7 hours in children who were referred and it ranged from 10 minutes to 5.5 hours with a mean of 1.86 hours among those who came by themselves. None of the children referred from primary and secondary centers had received even the first 10 vials of ASV. One child had cardiac arrest at admission and was revived with CPR before ASV. 10 children had respiratory failure and were intubated for ventilator support. The time interval between time of bite and administration of ASV among children who needed intubation was higher than those who did not need intubation (4.03 hours versus 3.6 hours). Duration of ventilation ranged from 6 hours to 99 hours. The mean duration of ventilation among the children was 27 hours. Overall 400 vials of ASV was used in 26 children 14 required 20 vials and 12 required 10 vials. One child died during the hospital stay. This was a 10 year old child with respiratory failure and inotrope refractory hypotensive shock admitted with a GCS of 3 and not improved with ASV, ventilator support and inotrope support.

Table 1: The clinical features of children at admission.

Clinical feature	N (%)	Clinical feature	N(%)
Ptosis	22	Abdominal pain	3
Local swelling/cellulite	19	Diplopia	2
Voice change	11	Local bleeding	2
Head lag	11	Dysphagia	2
Hypotonia	10	Hemetemesis	1
Vomiting	8	Epistaxis	1
Shock at admission	6	Fever	2

Of the 26 children, only one child did not have signs of envenomation at admission and subsequently developed signs of envenomation requiring ASV administration at 6 hours of admission. Overall 18 children developed reactions following ASV. Among the 16 children referred to our institute 11 of them had ASV reactions (68.7%) versus 7 of the 10 who were not referred (70%). Rashes were encountered in all 18 children. Rashes were encountered as early as 4 minutes of ASV and all them were within the first 30 minutes of ASV. Angioedema, cough, breathlessness was encountered in one child each during the study. Shock with hypotension was encountered in 9 children (34.6%) following ASV. Inotropes were given in the form of adrenaline infusion in children who required more than 2 doses of adrenaline. Hypotensive shock or need for more than 2 doses of adrenaline were considered as indications for adrenaline infusion. 13 children required adrenaline infusion for therapy during hospital stay. Two children needed intubation post ASV therapy. One child had rigors with fever at 1 hours of infusion. ASV reactions have been summarized in Table 2. However one child died in this study group with refractory shock and persistent altered sensorium.

Table 2: The ASV reactions.

Adverse reaction	N (%)	Adverse reaction	N (%)
Rash	18	Cough	1
Tachycardia	18	Tachyarrythmia	1
Itching	10	Vomiting	1
Shock	9	Breathlessness	1
Palpitations	4	Headache	1
Restlessness	2	Sweating	1
Angioedema	1	Fever /rigor	1
Feeling of pins needles	1	Diarrhea	1

DISCUSSION

Snake bite envenomation in pediatrics is associated with increased morbidity and mortality. Occupational hazard is the contributory factor in adults with snake envenomation. However in children majority of the time it is accidental and children may not always present with history of snake bite. In this study of 26 children neurotoxic envenomation was the commonest accounting for 77% of the children. However studies done elsewhere has shown predominance of hemotoxic bites. Studies by and by Sankar et al had shown that the incidence of neurotoxic bites to be 18% and by kumaravel et al has shown that neurotoxic envenomation to be in 9%.[4,5] Snake envenomation has been a neglected health care hazard in children and this study group is much different from other studies where more of hemotoxic envenomation has been reported. In this group majority of the envenomation was neurotoxic and nearly 38% needed ventilator support. Though two thirds of these children were referred they were not started on ASV in majority. The specific treatment of ASV was not given in these children as they reached the nearest health care facility. Children who were started on ASV developed rashes/ itching or hypotension and were referred with injection pheniramine maleate and dexamethasone. None of these children were administered injection adrenaline. Ptosis, hypotonia, areflexia and head lag were the major

presentation in these children. Compared to other studies in literature where hemotoxic envenomation is the commonest, this study has predominant neurotoxic envenomation and whether this has any implication on the higher occurrence of ASV reactions need to be studied.

The occurrence of ASV reactions was 70%. However the occurrence of ASV reactions varies across studies. Studies from elsewhere has shown that among children the rates to be as follows.1.2% by Kshirsagar, 6% by Kumaravel et al, 4% by pore et al.[2,5,6] Studies from Bangladesh has shown higher rates of reactions. It is possible to have anaphylactic and pyrogenic reactions commonly after administration of polyvalent anti-snake venoms. Seneviratne et al analyzed 28 patients in Sri Lanka and observed that 50% of them had anaphylactic reactions as well as 63% developed pyrogenic responses that occurred when diluent water employed was other than that one provided by manufacturer.[7] The percentage of anti-snake venom reaction cases was much higher up to 88.57%, pyrogenic reaction was 80.64% and anaphylaxis was 64.51%.[8] Delayed reaction in the form serum sickness was not reported in our study. The criteria to define serum sickness were pre-defined as three or more of fever, erythematous rash, urticaria myalgia, arthralgia, headache, malaise, nausea and vomiting 5-20 days post-antivenom.[9] Among the acute adverse reactions, all children had rashes to begin with. Predominantly the rashes were encountered in the trunk followed by the extremities and face. Studies in literature have shown urticaria to be the common feature in ASV reactions. Nearly 80% of anaphylactic reactions were due to urticaria.[8] All reactions had occurred within 30minutes of the commencement of ASV. Reactions had started as early as 4 minutes of starting ASV in this group. The average interval observed was 28 minutes. Literature evidence has shown the earliest response was recorded 10 minutes after the ASV administration (25 mL) while the delayed one occurred 50 minutes later (100 mL) 8. Theakeson et al documented that 33% cases of anaphylactic responses 50 minutes after the initial ASV dose.[10]

ASV is associated with early anaphylactic reactions, pyrogenic reactions and late serum sickness.[11] Early anaphylactic reactions: occur within 1-180 minutes of ASV and vary from mild rashes, cough, vomiting, abdominal colic, diarrhea, to serious bronchospasm, shock and cardio respiratory arrest. Majority is due to complement mediated mechanism or Fc fragment or mass cell stimulation. Pyrogenic reactions like fever rigor and hypotension develop 1-2 hours after starting ASV therapy due to pyrogenic contamination of ASV and diluting fluid.

In this series of cases 10 of them required more than one dose of adrenaline and 9 of them required adrenaline infusion to continue with administration of ASV. Literature has shown that among the 35 children, eighteen patients that had presented anaphylactic reactions were managed by a single dose of intramuscular adrenaline while two patients required second dose8. In the present study, One child in the group complained of persistent severe cough and one with breathlessness which were considered as severe reaction. All children completed 20 vials of ASV. Occurrence of reactions delayed the completion of ASV due to these interventions. Adverse effects of the ASV are common, and anaphylaxis can be fatal. Increasing the safety of treatment with antivenom serum for snake bite victims is, therefore, a matter of high priority. The dose of ASV and its influence the incidence of ASV reactions as shown by Srimannarayana et al where the occurrence of reaction were 8 in 30 versus 8 in 60 high versus low adverse reactions while those by Tariang et al has shown that low and high dose ASV had similar rate of adverse reactions.[12,13]

The occurrence of rashes, itching, tachycardia following ASV was the reason for referral in 8 children. None of the children had received the appropriate treatment for anaphylaxis in the form of IM adrenaline. Injection hydrocortisone, pheniramine maleate, dexamethasone atropine and IV fluids were the treatment received at the referral center prior to shifting. Three children were referred on endotracheal intubation prior to referral. The above treatment and referral pattern clearly indicates that the awareness about management of anaphylaxis needs to be created urgently among the primary and secondary level health care centers. The delay in administration of ASV due to referral and inadequate management of ASV reactions could be a reason for higher incidence of respiratory failure. Higher rate of respiratory failure was noted even among the children who were admitted without referral. However the mean duration of bite to ASV commencement in the referred and non-referred group was 3.7 hours and 1.86 hour respectively. Children referred had an undue delay in getting ASV completed and this is a consequence of inadequate management of ASV reactions in this group of children. Had these children been treated appropriately at the referral center for ASV reactions, this would have reduced the time interval between time of bite and ASV administration and further complications due to ongoing envenomation. It is well known that delay in administration of ASV will make much of the venom to be bound and the ASV may not be useful later. The ASV used in this study was liquid form of the vaccine and throughout the study duration 3 batches of vaccine was used sequentially and the reactions did not vary with the batch of ASV used in the study. ASV is produced in both liquid and lyophilized forms. Liquid ASV requires a reliable cold chain and refrigeration and has a two-year shelf life. Lyophilsed ASV in powder form has 5-year shelf life and requires only to be kept cool.

Current protocols do not recommend test dose for ASV administration as they are not predictive of anaphylaxis or late occurrence of serum sickness.[14,15] Since reactions

to presently available polyvalent ASV is unevitable, we need to identify strategies to prevent its occurrence along with appropriate timely management. Standard guidelines exist for management of ASV anaphylaxis. None should die of reaction to ASV as well as snake envenomation. Medical personnel should never refrain from ASV for fear of reactions though life threatening. Preparedness for anticipated ASV reaction is part of ASV administration. Despite adequate treatment reaction to subsequent dose ASV cannot be prevented, may be a change of batch of ASV can be attempted. The dose of ASV and the speed of administration of ASV influence the reaction to ASV. However at present evidence for prevention of anaphylaxis by various premedications is controversial16. Premedication with drugs like adrenaline, steroids, pheniramine maleate have been tried individually and in combination. Adrenaline was found to significantly reduce severe reactions to antivenom by 43% (95% CI 25-67) at 1 hours and by 38% (95% CI 26-49) up to and including 48 hours. Hydrocortisone and promethazine did not. Adding hydrocortisone negated the benefit of adrenaline.[17] However steroids have been used post ASV to prevent serum sickness in Australia.[18] Studies by williams et al had shown adrenaline to be effective. Reaction rates were significantly ($p < or = 0.005$) lower in adrenaline premedicated patients (7.7%) compared to patients premedicated without adrenaline (28.3%).[19] Cochrane review on this topic by Nuchpraryoon et al had identified adrenaline to be a prophylactic drug while antihistaminics are not found to be useful.[20]

It is a surprise to note that snake bite poisoning is not a priority for health research in the developing country like India. Monovalent antivenoms which are regionally specific is essential to reduce the existing high mortality. Polyvalent antivenoms were involved in 79% of recorded reaction cases, whereas monovalent ones were implicated in only 12.9%. This statement justifies the use and importance of monovalent anti venoms over polyvalent ones18.Until such venoms are available based on the regionally prevalent snake species, we need to have evidence based literature on premedication therapy to reduce the incidence of ASV reactions which are life threatening in children.

The findings of this study reveal the following

- Neurotoxic envenomation is much more common children in this semi urban referral institute
- 70% of children receiving ASV develop reactions.
- Urticaria and rashes were the common ASV reactions
- 50%of children with reactions were severe in the form of shock
- Occurrence of reactions delay the timely infusion of ASV more so in children referred from primary or secondary institutions
- Primary and secondary health care facilities lack ability to manage ASV induced reactions effectively before referral.

Recommendation

- Medical personnel in primary and secondary level health care facilities need to manage ASV reactions at their centers rather than referral which would prevent undue delay in administration of ASV
- The role of premedication with drugs in minimizing the reactions to ASV need to be explored. There is an urgent need to have evidence based guidelines on such protocols
- Venom detection kits and monovalent anti venoms based on prevalent snake species might help reduce the mortality and morbidity in children with snake bite.

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