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ORIGINAL ARTICLE

ROLE OF ADRENALINE PREMEDICATION IN REDUCING ANTI-SNAKE VENOM INDUCED ADVERSE REACTIONS IN CHILDREN

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ABSTRACT

Aim: This prospective study was undertaken to identify whether premedication with subcutaneous adrenaline at a dose of 0.01 mg/kg of 1 in 1000 solution is effective in reducing the adverse reactions following anti-snake venom (ASV) administration in children.

Methods and Material: This prospective study was conducted over 3 years from 2015-2018 in children who received ASV injection at the pediatric intensive care unit (PICU) of our institute. Children who had received ASV elsewhere prior to referral were excluded from the study. Those children recruited between 2015 and 2016 were considered as group 1 without premedication and those recruited between 2017 and 2018 were considered as group 2 with adrenaline premedication. Study parameters included the type of snake envenomation and adverse reactions following ASV administration in both groups. Children were followed up till 12 weeks after discharge from the hospital.

Results: Among the 65 children admitted during the study period, 9 children did not have signs of envenomation, 5 children had already received ASV prior to referral, and hence 51 children were recruited for the study of which 30 children did not receive premedication (Group 1) and 21 children received premedication (Group 2). Overall incidence of adverse reactions was significantly lower in the premedication group in comparison to the group with no premedication (8/21 vs 18/30) (p=0.04). Fever (none in group 2 vs 6/30 in group 1 with p 0.032), rashes (8/21 vs 18/30, p=0.04), and anaphylaxis (4/21 vs 14/30, p=0.038) were significantly lower following premedication with subcutaneous adrenaline.

Conclusion: Premedication with subcutaneous adrenaline leads to lesser adverse effects in children receiving ASV.

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Introduction

Snake envenomation is a common medical emergency in children, more so in the rural and semi-urban settings. Children may or may not present with a history of snakebite and have features of snake envenomation like acute descending flaccid weakness of limbs or isolated respiratory difficulty or bleeding manifestations.[1] Administration of anti-snake venom (ASV) is the definitive treatment for venomous snake bites.[2] ASV is an immunoglobulin that is enzyme derived. Monovalent antivenom neutralises one species and in India, polyvalent venom is used and is produced against 4 important venomous snakes in the region namely cobra, Indian common krait, Russel's viper and saw-scaled viper.[3] This is available as both lyophilized powder and as liquid form. Administration of ASV is known to be associated with severe adverse reactions. Incidence of adverse reactions varies from 10% to as high as 69% in different regions.[4,5] Rashes and itching are common adverse events encountered following ASV administration.[5] A presumptive diagnosis of snake envenomationis undertaken especially in children presenting with krait bites in the early morning hours with respiratory difficulty and unresponsiveness.[1] These children may not have a history of snakebite or any circumstantial evidence of having seen a snake in the vicinity. In such situation's, injection ASV is administrated based on clinical suspicion and there is no definite laboratory test as of now to confirm or rule out snake envenomation. If the clinical diagnosis is suggestive of snake envenomation, this warrants administration of ASV as a life-saving therapy. Occurrence of any life-threatening anaphylaxis following presumptive ASV administration in this scenario could be a difficult task to manage and counsel caregivers. The adverse reactions vary from mild rashes

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with itching to severe life-threatening anaphylaxis with shock. Early reactions are encountered between 10-180 minutes of ASV administration.[6] Literatures earch revealed various interventions like premedication with injection pheniramine maleate, hydrocortisone and adrenaline either alone or in varied combination to prevent these reactions.[7,8] However, the results are inconsistent for a definite recommendation of any of these drugs as premedication. Standard protocols for adrenaline premedication for ASV administration are available in recent literature and are based on adult studies.[3] To our knowledge, there are no publications on adrenaline use as premedication in the prevention of ASV reactions in children. This study was undertaken to identify the effectiveness of premedication with subcutaneous (SC) adrenaline in reducing the allergic reactions/anaphylaxis following ASV administration and to study the safety of subcutaneous adrenaline as a premedication prior to ASV administration.

Methods & Materials

This was a prospective study undertaken between January 2015-December 2018 to evaluate the usefulness of SC adrenaline as a premedication in reducing the adverse reactions following administration of ASV among children with features of snake envenomation in the pediatric intensive care unit (PICU) of a tertiary care semi-urban referral center. All children admitted with or without a history of snakebite but with features of snake envenomation such as hemato-toxicity or neurotoxicity and planned for the administration of injection ASV were included in the study after informed consent of the caregivers. Study was undertaken after institutional ethics committee approval. Children who were treated elsewhere with a diagnosis of snake envenomation and referred to this institute but whose details were not available were excluded from the study. History, clinical examination, ASV dose, events/adverse reactions following ASV, duration of intensive care unit stay, need for surgical intervention, hospital stay, and outcome were studied. Those children recruited between 2015 and 2016 were considered as group 1 without premedication and those recruited between 2017 and 2018 were considered as group 2 with adrenaline premedication. Adrenaline

Table 1. Baseline parameters among the two groups

Study parameter	Group 1 (n=30) without premedication	Group 2 (n=21) with premedication	P value
Mean age (years)	6.78 ± 3.26	6.92 ± 3.43	0.85
Male:Female ratio	1.46	1.33	1.0
Hemato-toxicity	4 (13.3%)	5 (23.8%)	0.24
Neurotoxicity	22 (73.3%)	15 (71.4%)	0.56
Localenvenomation	23 (76.6%)	14 (66.6%)	0.31

Table 2. Adverse reactions between both the groups

Study parameter	Group 1 (n=30) without premedication	Group 2 (n=21) with premedication	P value
Overall reactions	21 (70%)	8 (38%)	0.04
Anaphylaxis	14 (46.7%)	4 (19%)	0.038
Tachycardia (post ASV)	9 (30%)	4 (19%)	0.51
Cough	4 (13.3%)	2 (9.5%)	1.0
Vomiting	2 (6.6%)	1 (4.8%)	1.0
Abdominal pain	2 (6.6%)	1 (4.76%)	1.0
Rashes	21 (70%)	8 (38%)	0.04
Vomiting	2 (6.6.%)	1 (4.8%)	1.0
Fever and rigors	6 (20%)	0	0.032
Shock	8 (26.6%)	4 (19%)	0.52
Inotropic support	8 (26.6%)	2 (9.5%)	0.096
ASV vials used	16 ± 1	19.4 ± 7.3	0.055
ICU Stay (hrs)	100.9 ± 57.2	18.7 ± 27.8	0.000
Mean duration of IV fluids for shock (hours)	33.92 ± 27.6	38.3 ± 16.2	0.29
Surgical intervention	13 (43.3%)	3 (14.3%)	0.02
Hospital stay (days)	16.8 ± 16.4	5.3 ± 3.3	0.019
Death	2 (6.6%)	1 (4.76%)	0.63

premedication was given to all children in group 2 at a dose of 0.01 mg/kg of 1 in 1000 solution SC as a single dose 10 minutes prior to commencement of ASV infusion. This did not delay the treatment with ASV as adrenaline was given subcutaneously once signs of envenomation were identified. As it was given during the time taken for preparation of ASV infusion there was no delay in ASV administration because of this intervention as a premedication. Lyophilised preparation of ASV was used for all children in the study group. Children were considered for ASV administration based on the features of neurotoxicity, hemato-toxicity, and local envenomation with evidence of ongoing envenomation signs as per World Health Organization (WHO) guidelines for management of snake bites.[3] ASV vials used in this study belonged to varied batches from the same manufacturers as they were supplied at the institute over the years from 2015 to 2018. Children were closely monitored for adverse reactions and were followed up to 12 weeks after discharge or death in case of mortality. Both early and delayed adverse reactions were studied in the group. Late reactions if encountered were studied by follow up after discharge. Study parameters included gender ratio, age, adverse reactions, fever with rigors, rashes, urticaria, itching, puffy eyelids, shock[9], anaphylaxis[10], pulmonary edema, stridor, cough, chest tightness, wheeze, bronchospasm, blood pressure fluctuations, hypoxemia (SPo2<94% in room air), syncope, abdominal pain, vomiting, and final outcome.

Children discharged home were advised to return for follow up if they pruritus, urticaria, arthralgia, lymphadenopathy, periarticular swelling, and neurological impairment including encephalopathy up to a period of 12 weeks. Complications like unexplained tachycardia, hypertension[9] and arrhythmias following SC adrenaline are observed in premedication group.[3] Clinical features not satisfying the criteria were considered as adverse reactions. Children who developed adverse events were promptly treated as per the unit przotocol for anaphylaxis and ASV therapy was completed.

Statistical Analysis: Comparison of the study parameters were undertaken among the two groups with and without adrenaline premedication by t-test for numerical data and Fischer exact test for nominal data. EPI Info™ 7 statistical software was used for statistical analysis. p values <0.05 was considered significant.

Results

Among the 65 children admitted during the study period, 9 children did not have signs of envenomation, 5 children had already received ASV prior to referral, and hence 51 children were recruited for the study. Thirty children were in group 1 without premedication and 21 children were in group 2 with premedication. Baseline parameters between both the groups were comparable (Table 1). Adverse reactions between the two groups are depicted in Table 2.

Children with premedication with adrenaline had a lesser need for surgical interventions like decompression, fasciotomy, and grafting (Table 1). Except for tachycardia, which is multifactorial in this group, none had any arrhythmia following premedication with adrenaline. None of the children had late adverse effects when followed up for 12 weeks.

Discussion

Literature review on prevention of adverse reactions to ASV administration is not conclusive. Various drugs alone or in combination have been tried with varying results. Adrenaline, hydrocortisone, chlorpheniramine maleate have all been tried but not uniformly convincing results exist for regular prophylaxis, especially in children with snake envenomation.[3,11,12,13] Studies in adults have raised concerns on the adverse events of premedication drugs.[14] Cochrane review reveals that subcutaneous adrenaline has been found to be more useful in preventing these reactions rather than antihistamines. Adrenaline (epinephrine) is the most widely used catecholamine drug for the prevention and/or treatment of early adverse reactions to antivenoms.[7,15] Studies have shown varied results with hydrocortisone either alone or with anti-histaminic.[8,16,17] However recent studies have favoured the use of premedication with adrenaline to reduce the ASV induced adverse reactions in adults.[3,18,19,20,21] Ideal dosing of adrenaline premedication needs to be assessed by larger trials in children.Adrenaline (epinephrine) is the most effective treatment for anaphylactic reactions, by reducing bronchospasm and capillary permeability.Mast cell activation and basophil triggering are opposed by adrenaline. Adrenaline is bothα and β adrenoceptor agonist.The α1 receptors if activated leads to arterial and venous vasoconstriction. The β receptor stimuli increases the cardiac output. Similarly, the receptors in the bronchial muscles results in bronchodilation.[22] Adrenaline as a prevent or has been licensed for use in anaphylaxis using pen injectors in people at risk for anaphylaxis.[23] However, the explanation as to how premedication with adrenaline could help reduce the adverse reactions needs to be assessed in future studies. The duration of hospital stay was less in the premedication group probably related to the adrenaline induced vasoconstriction and capillary permeability, thereby minimising the venom induced tissue damage and leading on minimal surgical interventions like excision, reconstruction and grafting. Premedication using adrenaline was found to reduce the overall adverse reactions like fever with rigors, rashes and anaphylaxis following ASV. The need for invasive surgical intervention, duration of PICU stay and the hospital stay were significantly lower in the premedication group. Occurrence of anaphylactic shock was not significantly reduced with premedication with adrenaline. Use of adrenaline premedication was found to be safe in children prior to ASV administration.

Conclusion

Premedication with subcutaneous adrenaline (0.01 mg/kg of 1 in 1000 solution) 10 minutes prior to ASV administration in children significantly reduces the occurrence of adverse reactions following ASV. Subcutaneous adrenaline premedication is safe in children. However, there is an urgent need for larger trials on efficacy and dose of adrenaline with adrenaline as premedication prior to ASV, in children for future recommendations.

Compliance with Ethical Standards

Funding: None

Conflict of Interest: None

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