Original Article

Low Dose Subcutaneous Adrenaline Pretreatment for Antisnake Venom Adverse Reactions Prevention

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ABSTRACT

Objective: To compare the frequency of patients who develop acute adverse reactions to antisnake venom after receiving low dose subcutaneous adrenaline with those receiving only placebo.

Study Design: Randomized controlled trial study.

Place and Duration of Study: This study was conducted at the Department of Medicine, Benazir Bhutto Hospital Rawalpindi from May 2019 to November 2019.

Methods: Ethical approval for the study was sought from Institutional Research and Ethics Forum of RMU. After obtaining informed consent, all the patients with systemic envenomation were given 0.25m1 of 1:1000 adrenaline (cases) or placebo(control) subcutaneously into forearm immediately before starting ASV infusion. Patients were then monitored for acute adverse reactions. To compare the proportion of acute adverse reactions between two groups Pearson's Chi-square test at 5% level of significance was applied. P- value of <0.05 was considered statistically significant.

Results: Total patients in study were 60 which were equally divided into two groups i.e. Placebo and study group. The mean age of the patients was 35.87 ± 14.55 years. The gender distribution showed that 35 (58.3%) patients were from the male gender. Regarding the adverse reactions, 21 (35%) patients developed the acute reactions. There was significant difference among groups in terms of adverse reaction (05 (16.67%) in adrenaline group versus 16 (53.33%) in placebo group, p value was 0.003).

Conclusion: The risk of adverse reactions due to asv is lower in group in which the low dose subcutaneous adrenaline was used as compared to placebo group. The data should be verified on larger scale study.

Key Words: Adolescent, adverse effects, Double-Blind Method, Epinephrine, Humans, Middle Aged, Prospective Studies, Snake Bites

Citation of article: Abid S, Abid QA, Shad I, Batool A, Hassan MS, Zahid H. Low Dose Subcutaneous Adrenaline Pretreatment for Antisnake Venom Adverse Reactions Prevention. Med Forum 2024;35(5):28-31. doi:10.60110/medforum.350506.

INTRODUCTION

Of 3000 snake species in world, 600 are venomous resulting in 2 million snake bite envenomation and 100,000 deaths per year.[1] In Pakistan there are 20,000 deaths per year.[2] Snakebite is a major health problem in the rural tropics.[3] Snake venom have an array of enzymes, proteins and toxins.[4]

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Received: April, 2023
Accepted: July, 2023
Printed: May, 2024

Highly venomous snake bite can cause necrosis around bite site, widespread bleeding, irreversible kidney damage and muscle paralysis.[1]

For snake bite envenomation, antisnake venom (ASV), is the mainstay of treatment.[5] ASV is mixture of antibodies, derived from animals mostly horses and sheep that effectively neutralize toxins which cause coagulopathy, hemorrhage and hemodynamic disturbances.[1] According to WHO adverse reactions to ASV are classified as early reactions occurring within first hour of ASV infusion and late reactions occurring between 5-20 days after treatment.[6] Antivenom commonly cause acute adverse reactions', which are mostly due to type 1 hypersensitivity complement activation and immunoglobulin aggregate including Fc.[4]

Reactions due to ASV in patient with snake bite cause considerable challenge to clinicians.[1] Most reactions are mild resulting in nausea, vomiting, headache, urticaria, fever but systemic anaphylaxis occurs in 40% of cases which is potentially fatal resulting in hypotension, cyanosis and altered level of consciousness.[7]

Anaphylaxis is severe, generalized hypersensitivity reaction which is rapid in onset and can cause death.[8] For prevention of acute adverse reactions pretreatment with hydrocortisone, antihistamine and adrenaline was done previously.

In anaphylaxis treatment adrenaline is drug of choice but there is no clear uniform policy for adrenaline pretreatment for prevention of acute adverse reaction to ASV.[9] In retrospective analysis conducted in Australia for pretreatment with adrenaline, antihistamines and steroids found to decrease adverse reactions to ASV from 12.5% to 3%. But the study did not differentiate between individual drug effectible study conducted in Sri Lanka showed 11% patients developed acute adverse reactions when received adrenaline pretreatment as compared to 43% patients who did not received adrenaline pretreatment.[9]

Snake bite envenomation tends to be major health problem in Pakistan. No study has been conducted locally to assess efficacy of adrenaline pretreatment in preventing ASV acute side effects. The rationale of this study is to increase safety of treatment with ASV in snake bite patients with low dose subcutaneous adrenaline premedication. The results of this study will helpful to treating physician in modifying current treatment practice as there was previously unclarity on pretreatment and will reduce the mortality due to fatal acute adverse reactions. Main objective was this research is to compare the frequency of patients who develop acute adverse reactions to antisnake venom after receiving low dose subcutaneous adrenaline with those receiving only placebo.

METHODS

A randomized controlled trial was conducted at department of medicine, Benazir Bhutto Hospital for the assessment of adverse effects of antisnake venom after receiving low dose subcutaneous adrenaline and placebo after obtaining ethical approval (R-14/RMU) from institutional review board of Rawalpindi Medical University from May 2019 to November 2019. A total of 60 patients were recruited by using non-random consecutive sampling with age range of 12 to 70 years; all patients were those who required anti snake venom after snake bite. Sample size was calculated by considering population proportion of acute adverse effects in adrenaline group = 0.1101 Population proportion of acute adverse effects in placebo group = 0.43[9] with power of test at 80% level of significance at 5 % and total sample size of 60 was calculated and were grouped into two groups accordingly. Pregnant females or those who have already received any treatment before admission or have any ischemic disease were excluded from the study.

After obtaining informed consent, all the patients with systemic envenomation were given 0.25m1 of 1:1000 adrenaline (cases) or placebo(control) subcutaneously into forearm immediately before starting ASV infusion. Patients were then monitored for acute adverse reactions. Blood pressure and pulse were checked every 15 minutes during infusion and 1 hour after end of infusion. If acute adverse reaction occurred, ASV was stopped and 0.5ml of 1:1000 adrenaline was given intramuscularly along with 200mg IV hydrocortisone and 25mg IV promethazine. Patients were followed till discharge. All the data was recorded on a specially designed Performa.

Statistical Analysis: Data was entered and analyzed using the Statistical Package for Social Sciences (SPSS version 21). All the categorical variables like gender, B.P, pulse, acute adverse reactions were described as frequencies and percentages, while for continuous variable like age, the mean along with standard deviation was calculated. To compare the proportion of acute adverse reactions between two groups Pearson's Chi-square test at 5% level of significance was applied. P-value of <0.05 was considered statistically significant. To control any effect modifier e.g. age, gender stratified Chi-square test was also applied.

RESULTS

The total patients in my study were 60 which were equally divided into two groups i.e. placebo and study group. The mean age of the patients was 35.87 ± 14.55 years. The age group was divided into two groups which were later on used for the stratification purposes. The distribution is given below in the graph. There was no significant difference among groups in terms of age distribution as p value was 0.174.

Table No.1: Assessment of Gender, Herat rate Blood Pressure and Adverse Reaction in Study Groups.

Parameter		**Group**		P-value[1]
		Adrenaline	**Placebo**	
Gender	Male	16 (53.33%)	19 (63.33%)	0.432
	Female	14 (46.67%)	11 (36.67%)	
Pulse	Bradycardia	16 (53.33%)	18 (60%)	0.602
	Tachycardia	14 (46.67%)	12 (40%)	
BP	Hypotension	12 (40%)	14 (46.67%)	0.602
	No	25 (83.33%)	14 (46.67%)	

Table No.2: Comparison of Adverse Reactions in Study Groups based on Age and Gender.

Parameter		Reaction	Group		P value[2]
			Adrenaline	Placebo	
Age	<40 years	Yes	03 (16.67%)	11 (61.11%)	0.002
		No	18 (85.71%)	07 (38.89%)	
	>40 years	Yes	02 (22.22%)	05 (41.67%)	0.350
		No	07 (77.78%)	07 (58.33%)	
Gender	Male	Yes	04 (25%)	12 (63.15%)	0.024
		No	12 (75%)	07 (36.84%)	
	Female	Yes	01 (7.14%)	07 (38.89%)	0.070
		No	13 (92.85%)	11 (61.11%)	

The gender distribution showed that 35 (58.3%) patients were from the male gender. Regarding the adverse reactions, 21 (35%) patients developed the acute reactions. Out of 60 patients, 34 (56.7%) showed bradycardia during BP monitoring while 26 (43.3%) showed hypotension. There was no difference between groups in terms of gender, pulse and BP distribution as p values were 0.432, 0.602 and 0.0602 respectively. There was significant difference among groups in terms of adverse reaction (05 (16.67%) in adrenaline group versus 16 (53.33%) in placebo group, p value was 0.003) as explained in table 1. The data was stratified according to age and gender. The results showed that the results were specific only for male gender and age group <40 years (p value 0.024 and 0.002 respectively) as explained in table 2.

DISCUSSION

The anaphylactic reactions are one of the most common encountered problems in emergency departments. The reaction is more pronounced and anticipated when some antisera is injected. The conditions like snake bites in which the benefits overweight risks are very tricky to deal with.[11] The management of snake bite is always involves the use of antisnake venom (ASV). The ASV may be generic or specie specific but is always associated with a wide range of adverse reactions.[12] The immune response to ASV involves the complement activation, cytokine production and mast cell degranulation.[13]

The adverse reactions can be classified into two major categories i.e. early and late. The major concern in emergency medicine is the early reactions.[6] To combat adverse reactions the use of adrenaline, hydrocortisone and promethazine is used during the active surveillance. The pretreatment with these medications involving low dose adrenaline is one the best remedy to prevent adverse reactions of ASV. These facts are very important in the areas of high incidence of snake bites and risks of more adverse reactions.[14]

The minor to moderate reactions to antivenoms are common and some of them reach up to severity. There are many studies which show that the acute adverse reactions can be reduced by the pre medications. A study reported in a study that the antivenoms in Australia has low risk of reactions only due to the fact that pre medications play a major role in this regard. He concluded that antivenoms in Australia are well tolerated with few adverse reactions. The use of premedication like antiallergics, adrenaline and oral steroids can reduce the reaction rate.[15]

In a study by Premawardhena, A. P., et al. the results showed that out of 56 cases who received adrenaline the acute adverse reactions were visible in 06 (11%) patients. The placebo group which contained 49 patients has 21 (43%) reactions rate (P=0.0002).[16] In my study the 05 (16.6%) and 16 (53.3%) patients showed the reaction in adrenaline and placebo groups respectively (p value 0.003). A study by de Silva et al showed that when adrenaline was compared with placebo, it reduces the reactions by 43% (95% CI 25-67) at 1 h and by 38% (95% CI 26-49) up to and including 48 h after ASV administration.[17]

In my study the data was stratified according to age and gender. The results showed that the results were specific only for male gender and age group <40 years (p value 0.024 and 0.002 respectively)

CONCLUSION

The risk of adverse reactions due to ASV is lower in group in which the low dose subcutaneous adrenaline was used as compared to placebo group. The data should be verified on larger scale study.

Author's Contribution:

Concept & Design of Study:	Seemab Abid
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Conflict of Interest: The study has no conflict of interest to declare by any author.

Source of Funding: None

Ethical Approval: No.R-14/RMU dated 21.04.2018.

REFERENCES

1. McGhee S, Finnegan A, Clochesy JM, Visovsky C. Effects of snake envenomation: a guide for emergency nurses. Emerg Nurse 2015;22(9):24-9.
2. Isbister GK, Jayamanne S, Mohamed F, Dawson AH, Maduwage K, Gawarammana I, et al. A randomized controlled trial of fresh frozen plasma for coagulopathy in Russell's viper (Daboia russelii) envenoming. J Thromb Haemost 2017; 15(4):645-54.
3. Stone SF, Isbister GK, Shahmy S, Mohamed F, Abeysinghe C, Karunathilake H, et al. Immune response to snake envenoming and treatment with antivenom; complement activation, cytokine production and mast cell degranulation. PLoS Negl Trop Dis 2013;7(7):e2326.
4. de Silva HA, Ryan NM, de Silva HJ. Adverse reactions to snake antivenom, and their prevention and treatment. Br J Clin Pharmacol 2016;81(3): 446-52.
5. Leon G, Herrera M, Segura A, Villalta M, Vargas M, Gutierrez JM. Pathogenic mechanisms underlying adverse reactions induced by intravenous administration of snake antivenoms. Toxicon 2013;76:63-76.
6. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117(2):391-7.
7. Sicherer SH, Simons FER, Section On A, Immunology. Epinephrine for First-aid Management of Anaphylaxis. Pediatr 2017; 139(3):e20164006.
8. de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, et al. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS Med 2011;8(5):e1000435.
9. Isbister GK. Antivenom efficacy or effectiveness: the Australian experience. Toxicol 2010; 268(3):148-54.
10. Daley BJ, Torres J. Venomous snakebites. JEMS 2014;39(6):58-62.
11. Senthilkumaran S, Menezes RG, Pant S, Thirumalaikolundusubramanian P. Acute acalculous cholecystitis: a rare complication of snake bite. Wilderness Environ Med 2013;24(3): 277-9.
12. Sundaraperumal R, Mohanasundaram K, Kumarasamy S. Acute coronary syndrome following snake bite: a report of three cases from a tertiary care hospital in rural southern India. Trop Doct 2012;42(3):171-3.
13. Satish R, Kanchan R, Yashawant R, Ashish D, Kedar R. Acute MI in a stented patient following snake bite-possibility of stent thrombosis - a case report. Ind Heart J 2013;65(3):327-30.
14. Kumar PK, Ahuja S, Kumar PS. Bilateral acute anterior uveitis and optic disc edema following a snake bite. Korean J Ophthalmol 2014;28(2): 186-8.
15. Deepak M, Basavaprabhu A, Ramapuram JT, Nithyananda C, Mahalingam S. Bilateral parotid enlargement following snake bite: a rare sign. Asian Pac J Trop Biomed 2013;3(2):154-5.
16. Wall C. British Military snake-bite guidelines: pressure immobilisation. J R Army Med Corps 2012;158(3):194-8.
17. Vithanage KK, Thirumavalavan K. A case of a sea snake bite resulting in fatal envenoming. Ceylon Med J 2012;57(4):174-5.