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Research Article

STUDY ON ACUTE ADVERSE DRUG REACTIONS OF ANTISNAKE VENOM IN A RURAL TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: Snake bite is a major occupational hazard especially in rural areas. Majority of the anti-venom reactions are wrongly attributed to envenomation. There is inadequate reporting of anti-venom reactions leading to the paucity of true data of morbidity and mortality. The aim was to evaluate the adverse drug reaction (ADR) profile of anti-snake venom serum (ASV) in a rural tertiary care hospital.

Methods: A prospective, observational study was conducted. A total number of 50 indoor cases of snake bites from May 2012 to January 2013 was included in the study, and the anti-venom reactions were assessed. In addition, basic epidemiological data and prescribing practices of ASV were also analyzed.

Results: The incidence of snake bite was more in males (64%) as compared to females (36%) attributed to their out dwelling lifestyle. Vasculotoxic snake bites were more common (46%) than neuroparalytic ones (44%). Mild envenomation was the most common presentation. A total of 31 (62%) patients who received ASV suffered from anti-venom reactions. The most common nature of the reaction was chills, rigors (23.53%) followed by hypotension (21.57%). 52.94% cases of adverse reactions were of early anaphylactic type followed by 45.1% cases of pyrogenic reactions. 43.14% of cases of anti-venom reactions were probable in nature, and 13.73% were certain in nature with World Health Organization-Uppsala Monitoring Centre classification of ADRs. By using modified Hartwig Seigel scale, 70.59% cases were mild in severity, and 5.88% were severe in nature. Most of the reactions were classified as not preventable with the Schumock Thornton criteria. All the reactions were classified as hypersensitivity reactions with Karch and Lasanga classification.

Conclusions: Present study showed a higher incidence of reactions to ASV at our institute. There was an inadequate documentation of clinical findings, investigations, and adverse reactions in most of the case papers.

Keywords: Anti-snake venom, Adverse drug reactions, Pharmacovigilance, Snake bite.

INTRODUCTION

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse drug reactions (ADRs) [1]. Recently, its concerns have been widened to include herbals, traditional and complimentary medicines, blood products, biological, medical devices, and vaccines. The pharmacovigilance program of India was initiated with a goal to ensure that the benefits of use of medicine outweigh the risks and thus safeguard the health of the Indian population. It has an objective of monitoring the safety of the drugs and creation of ADR database for the Indian population [1].

Snake bite is a common, neglected and frequently devastating environmental and occupational disease, especially in rural areas of tropical developing countries. It is a major public health problem in India with estimated annual snake bite incidence of about 2,50,000 out of which approximately 20% bites result in significant envenoming which require anti-snake venom (ASV) administration [2]. The snake bite associated morbidity is estimated to be about 1.4-68/1 lakh population, mortality about 1.1-2.4/1 lakh and case fatality rate of 1.7-20% [3]. It is estimated that between 35,000 and 50,000 people die of snakebite in India each year [4]. Early in 2009, snake-bite was included in the World Health Organization (WHO's) list of neglected tropical diseases [5]. Like other neglected diseases, snakebite envenoming has received little attention from health authorities, pharmaceutical companies, or research funding agencies. Snake-bite is a common occupational hazard of farmers, plantation workers who are generally from low socio-economic status, resulting in tens of thousands of deaths each year and many cases of chronic physical handicap.

ASV and its rational use is the only definitive treatment to neutralize the venom in circulation and tissue fluid to save the life in snake bite cases. Anti-venom is an immunoglobulin (Ig) usually pepsin refined F $(ab)_2$ fragments of IgG purified from the serum or the plasma of a horse or sheep that has been immunized with the venom of one or more species of snakes. In India, only polyvalent ASV is available. The anti-venins are produced against 4 most important venomous snakes of India - Naja naja (Indian Cobra); Bungarus caeruleus (Indian common krait); Daboia russelii (Russell's viper); and Echis carinatus (Saw-scaled viper). Each milliliter of polyvalent ASV produced in India neutralizes 0.6 mg dried Indian cobra venom, 0.45 mg dried common krait venom, 0.6 mg of dried Russell's viper venom and 0.45 mg of dried saw-scaled viper venom [6,7].

Usually more than 20% cases develop either early (within few hours) or late (5 days or more) allergic reactions following ASV administration [4]. ASV usage remains a very risky job. The deaths due to ASV reactions are wrongly attributed to envenomation. In addition, the significant problem of acute adverse reactions to ASV is compounded by a lack of appropriate recommendations regarding prevention, diagnosis, and management of such reactions [8].

Detection and management of anti-venom reactions are a challenging medical problem that deserves special attention. Considering the prevalence of snake bites and severity of the problem at rural setup the present study was planned to evaluate the ADR profile of ASV in a rural tertiary care teaching hospital.

METHODS

Ethics

An observational study was conducted in pharmacovigilance center at Swami Ramanand Teerth Rural Government Medical College, Ambajogai, Maharashtra. The ethical approval was obtained from Institutional Ethics Committee prior to initiation of the study.

Patients

A total number of 50 indoor cases admitted from May 2012 to January 2013; with the diagnosis of poisonous snake bite that would require ASV were included in the study. The data were collected on a case record form. The first section of the data included demographic data such as initials of patient, age, gender, weight, occupation, and address. The second section was regarding the documentation of snake bite like type of snake bite, initial clinical presentation of the patient, intra-dermal sensitivity test done or not, 20 minutes whole blood clotting test (WBCT), dose, route, and frequency of administration of ASV.

Signs of adverse reactions

The anti-venom reactions were documented and classified as early anaphylactic, endotoxic (pyrogenic), and late (serum sickness type) reactions. The management of anti-venom reactions was also recorded. The data were filled on suspected ADR reporting form by Central Drug Standard Control Organization. The reactions were assessed by seriousness (death, life-threatening, hospitalization-initial or prolonged, disability, and required intervention to prevent permanent damage/impairment) and outcome (fatal, continuing, recovered and recovering). The outcome of the cases was analyzed under headings of recovery, referral, and mortality.

RESULTS

Patient demographics

Of the 50 patients, who received anti-venom, 32 (64%) were male and 18 (36%) female. This can be attributed to the out-dwelling lifestyle and occupational outdoor stay of males. Incidence of snake bite was the most common in the age group of 21-40 years (48%), followed by ≤20 years (26%) (Table 1). The incidence of anti-venom reactions was the highest in the age group of 21-40 years. We found the incidence of vasculotoxic snake bites (46%) was comparable to the neuroparalytic snake bites (44%).

Anti-venoms used, dosage forms and routes of administration

The ASV used at our setup during the study duration was manufactured by, Haffkine Biopharmaceutical Company Ltd. Mumbai, VINS Bioproduct Ltd. Hyderabad and Bharat Serum and Vaccines Ltd. Mumbai. The lyophilized anti-venom was reconstituted with 10 ml water to 10 ml of ASV. The dose of ASV largely depends upon the signs of systemic envenomation and severity of the bite. In our setup, the dose of ASV used ranges from 50 cc to 200 cc depending upon signs and symptoms of the patient. The most commonly used loading dose of anti-venom was 100 ml. The ASV was diluted and infused intravenously at a constant rate over a period of about 1 hr.

Intradermal skin testing to predict anti-venom reaction prior to administration of ASV?

Skin/conjunctival hypersensitivity testing does not reliably predict early or late anti-venom reactions as they are mediated by direct activation of complement system and not mediated by IgE and is not recommended [4,9-11]. However, in our study, we found that in about 86% of cases the skin hypersensitivity test was performed prior to initiation of ASV therapy. Skin testing only delay the administration of ASV and can themselves be sensitizing [4,9,11].

Adverse anti-venom reaction rates

A total of 31 patients (62%) who received ASV suffered from anti-venom reactions. The total number of ADRs recorded were 51; out of which 27 (53.94%) were of early anaphylactic type and 23 (45.1%) were pyrogenic in nature as per the WHO classification. The most common presentation of reaction were chills, rigors (23.53%) followed by hypotension (21.57%) (Fig. 1).

As per the World Health Organization-Uppsala Monitoring Centre classification of ADRs, the maximum number of anti-venom reactions were "probable (43.14%)" followed by "possible (41.8%)" and "certain (13.72%) (Table 2)".

The anti-venom reactions were classified as mild, moderate, and severe as per the modified Hartwig Siegel scale. Our study revealed that the maximum number of anti-venom reactions were mild in nature (70.59%) (Table 3).

Majority of the reactions were "not preventable" by Schumock Thornton criteria; and "hypersensitivity" in nature by Karch and Lasanga classification of mechanism of ADRs. All anti-venom reactions but one was "expected" in nature (Table 4).

Some investigators believe that ASV reactions are seen more in hemotoxic bites than neurotoxic ones. In our study, there was a higher

Table 1: Age and gender wise distribution of anti-venom reactions

Age (years)	Gender	N (%)		Total
		Reaction present	Reaction absent	
≤20	Male	6 (19.35)	2 (10.53)	13
	Female	3 (9.68)	2 (10.53)	
21-40	Male	7 (22.58)	8 (42.11)	24
	Female	9 (29.03)	0 (00)	
41-60	Male	2 (6.45)	2 (10.53)	7
	Female	3 (9.68)	0 (00)	
>60	Male	0 (00)	5 (26.32)	6
	Female	1 (3.23)	0 (00)	
Total		31	19	50

Table 2: Classification of ADR according to WHO-UMC classification

WHO-UMC class	Number of anti-venom reaction	%
Certain	7	13.72
Probable	22	43.14
Possible	21	41.18
Unclassified	1	1.97

WHO-UMC: World Health Organization-Uppsala Monitoring Center, ADR: Adverse drug reaction

Table 3: Classification of severity according to modified Hartwig Siegel scale

Severity	Number	%
Mild	36	70.59
Moderate	12	23.53
Severe	3	5.88

Table 4: Classification of preventability by Schumock Thornton criteria

Reaction	Number	%
Preventable	0	0
Not preventable	51	100

incidence of anti-venom reactions in cases of vasculotoxic snake bites (54.84%) as compared to neuroparalytic snake bites (38.71%).

DISCUSSION

Role of anti-venom

The only specific antidote to the toxins in snake venom is hyperimmune globulin from an animal that has been immunized with the appropriate venom [12]. The introduction of serum anti-venom by Albert Calmette in 1895 for the treatment of envenoming was quickly accepted without formal clinical trials [13]. More than a century later, anti-venoms are considered as essential drugs.

ASV is prepared from horse serum and is associated with allergic reactions which may result in anaphylaxis and even death. It is costly, and there is a constant shortage of ASV, particularly in rural and underdeveloped parts of India. Thus, ASV should be used only when there is a possibility of circulating venom in the body and not to all snake bite cases. However, early administration of ASV is essential to neutralize the maximum circulating venom before it is fixed in the tissue. Therefore, it should be given to cases with evidence of systemic envenomation as early as possible. Development of enlarged tender lymph node draining the bitten limb is an early manifestation of poisonous snake bite needing ASV therapy.

Adverse reactions to anti-venom and its prevention and treatment

Early anaphylactic reactions

It usually occurs in 10-180 minutes of starting anti-venom. It includes urticaria, itching (often over the scalp), cough, nausea, vomiting, abdominal colic, diarrhea, and tachycardia. Minority of cases present with fatal anaphylaxis-hypotension, bronchospasm, and angioneuritic edema. They occur due to direct activation of complement by IgG and residual FC fragment or direct stimulation of mast cells and basophils by antivenin proteins. They are not IgE mediated, type I reactions.

Pyrogenic reactions

It usually develops 1-2 hrs after starting ASV therapy. Fever, rigors, chills, hypotension are the presenting features. They are due to the pyrogenic contamination of ASV and diluting fluid.

Late serum sickness type reactions

It develops in 1-12 days after antivenin therapy (mean 7 days). Clinical features include fever, nausea, arthralgia, myalgia, arthritis, mononeuritic multiplex, recurrent urticaria, lymphadenopathy, neuritis, and even encephalopathy. They usually respond to oral antihistamine.

Our study showed a higher incidence of reaction to ASV as compared to WHO literature, most of which were of early anaphylactic type. The anti-venom reactions were treated with adrenaline, anti-histaminics, and systemic steroids.

20 minutes WBCT (20 WBCT)

This very useful and informative bedside test requires very little skill and one apparatus- clean, dry glass vessel. If the blood is still liquid (un-clotted) after 20 minutes and runs out, the patient has hypofibrinogenemia as a result of venom-induced consumption coagulopathy. This test is an important parameter for initiation and repetition of ASV in snake bite cases. In India, whole blood clotting time of more than 20 minutes is virtually diagnostic of viper bite and rules out elapid bite. However, our study has shown that in about 26% cases of vasculotoxic snake bites, 20 WBCT was not done, and it was done only in 18% cases of undiagnosed snake bites, indicating a poor management protocol.

Snakebite injuries occur most frequently in rural areas of tropical developing countries where access to and quality of health care services create difficulties both for the prompt administration of anti-venom and for the treatment of anti-venom-related reactions [14]. However, as our institute is a rural area-based tertiary care hospital, the mean average journey time to hospital is <3 hrs, ranging from 30 minutes to 24 hrs,

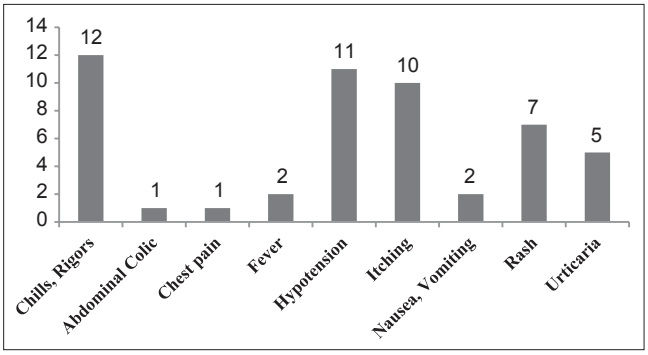

Fig. 1: Frequency of anti-venom reactions

which made it possible to manage the cases of snake bites early. The outcome of snake bite cases is more favorable owing to the continuous and adequate supply of ASV and trained staff.

CONCLUSION

This study provides insight into current clinical management of snake bite in rural health centers and provides incidence and severity of anti-venom reactions. We plan to use the results of this study to conduct a prospective trial for anti-venom premedication strategies in India.

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