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Research Article

STUDIES OF ADVERSE DRUG REACTION PROFILE OF ANTI-SNAKE VENOM AT DISTRICT GENERAL HOSPITAL**Mulchand Shende^{1*}, Sneha Gawali², Kanchan Bhongade², Vivek Bhuskade², Abhijit Nandgaonkar²**¹Department of Pharmaceutics, Government College of Pharmacy, Kathora Naka, Amravati, Maharashtra- 444604, India.²Pharm. D. Student, Government College of Pharmacy, Kathora Naka, Amravati, Maharashtra- 444604, India.**Abstract:**

Snake bite is a common predominant problem of the rural and periurban areas, neglected and frequently devastating environmental and occupational disease, especially in rural areas of tropical developing countries. This study aimed to investigate of the adverse drug reaction profile of anti-snake venom (ASV) in a district general hospital. An observational study was conducted in hospital for six months. A total number of 142 indoor case papers of snake bite from October 2016 to April 2017 were observed and retrieved from the record section. The antivenom reactions were assessed and prescribing practices of ASV were analyzed. It was observed that snakebites occur especially among active workers like farmers, plantation workers and laborers. The incidence of ASV reactions was higher in male (28) patients than female (15) patients in the age group of 21-40 years. Neuroparalytic snake bites were more common (44.18%) than vasculotoxic ones (41.65%). A total of 43 (30.28%) patients who received ASV suffered from antivenom reactions. The most common nature of reaction was chills, rigors (69.56%) followed by itching, urticaria, nausea and vomiting (34.8%). 10-15% patients suffered from moderate to severe reactions like hypotension and sudden respiratory arrest. ASV adverse drug reactions were more with 10 vials dose, followed by 5 vials dose, 3 vials dose, 15 vial doses and 8 vials dose. Our study showed a higher incidence of reactions to ASV at district hospital.

Key words: Snake bite, Envenoming, anti-snake venom (ASV), Antivenom reactions, Anaphylaxis**Corresponding Author:****Mulchand Shende,**Department of Pharmaceutics,
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INTRODUCTION:

Snake bite is a common, neglected and frequently devastating environmental and occupational disease, especially in rural areas of tropical developing countries [1]. According to WHO, in India 30,000 per annum is estimated the highest snake bite mortality in the world. There are about 236 species of snakes in India. Most of them are non-poisonous and their bites, apart from causing panic reaction and local injury do not harm the patient. However, there are 15 varieties that are poisonous and four among them, namely the cobras, the russell's viper, the saw-scaled vipers and the kraits are the most common [2]. Snakebite is a predominant problem of the rural and periurban areas. Most of the fatalities are due to the victim not reaching the hospital in time. Most of these fatalities are preventable. The community is not well informed about the occupational risks and simple measures that can prevent a bite. It continues to adopt harmful practices such as tourniquets, cutting and suction, herbal remedies, quackery etc. These are not only ineffective but also dangerous. Although total number of bites may be more than 5-6 lakhs but only 30% are venomous bites. Clinical effects of envenoming by same species of snake are almost similar except a few regional variations. Kraits are active during night hours, often biting a person sleeping on floor bed. Maximum viper and cobra bites occur during the day or early darkness, while watering the plantation or walking bare foot in grown grass or soybean crops. The high fatality due to Krait bite is attributed to the non-availability of anti-snake venom (ASV), delayed and inappropriate administration of ASV, lack of standard protocol for management and inexperienced doctors and non-availability of ventilator or bag and valve [3]. It is a major public health problem in India with estimated annual snake bite incidence of about 250,000 out of which approximately 20% bites result in significant envenoming which require anti-snake venom administration. It is estimated that between 35,000 to 50,000 people die of snake bite in India each year [1]. Anti-snake venom (ASV) and its rational use is the only definitive treatment to neutralize venom in circulation and in tissue fluid to save life in snake bite cases. Antivenom treatment for snake bite was first introduced by Albert Calmette at the Institute Pasteur in Saigon in the 1890s [4]. Antivenom is an immunoglobulin usually pepsin refined F(ab)₂ fragments of IgG purified from the serum or the plasma of a horse mule or donkey or sheep that has been immunized with the venom of one or more species of snakes. Specific antivenom implies that the anti venom has been raised against the venom of the snake that has bitten the patient and that it can therefore be expected to contain specific antibody

that will neutralize that particular venom and perhaps the venoms of closely related species (paraspecific neutralization). Monovalent (mono specific) antivenom neutralizes the venom of only one species of snake. Polyvalent (polyspecific) active neutralizes the venoms of several different species of snakes, usually the most important species, from a medical point of view, in a particular geographical area [5]. Anti snake venom treatment is the only specific treatment, should be given as soon as it is indicated. It may reverse systemic envenomation abnormality even when this has persisted for several days or, in the case of haemostatic abnormalities, persisting for two or more weeks. The dosage required varies with the degree of envenomation. In India only polyvalent ASV is available. The antivenins are produced against four most important venomous snakes of India; Indian cobra, Indian common krait, Russell's viper and Saw-scaled viper. Each ml 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 [8]. 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. Considering the prevalence of snake bites and severity of the problem at rural and periurban areas setup the present study was planned to evaluate the commonly occurring adverse drug reaction profile of ASV in district general hospital throughout six months.

MATERIALS AND METHOD:

An observational, non-interventional study was conducted for six months at government district general hospital, Amravati under pharmacy practice centre of Pharm.D at Government College of Pharmacy, Amravati, Maharashtra. Patient was informed about the purpose of the study and written consent was taken prior to their participation in the study. Ethical considerations including obtaining permission from the Ethics Committee of the Government College of Pharmacy to provide the management of hospitals, informed consent to participate in research of samples, ensure the confidentiality of the information received and used only for research purposes were fully met.

Inclusion and exclusion criteria

Patients in all age group of snake bite patient along with any other disease condition admitted in casualty, medicine wards and intensive care unit (ICU). Patient admitted for suspected snake bite who has not received anti-snake venom (ASV) were excluded.

Data source, record proforma and data analysis

Patient data relevant to the study has been collected from treatment charts/ case sheets, laboratory reports and patient or patient's caregiver's interview by using patient data collection form. It includes the patient demographics data (name, age, gender, area (urban or rural) and occupation, the dosage regimen (dose form and frequency), duration of therapy, duration of hospitalization, laboratory data, adverse drug reaction to ASV, type of bite, site of bites. The data generated in this study were analyzed for ADR of ASV, documentation and reporting of ADRs, appropriateness of drug, dose, frequency and duration.

Patients

Records of total number of 142 indoor cases admitted from October 2016 to April 2017 and data was collected on a prevalidated case record proforma. Out of which, 142 cases in whom ASV was administered due to systemic envenomation were included in the study results.

Signs of adverse reactions

The antivenom reactions were documented and classified as early anaphylactic, endotoxic (pyrogenic) and late (serum sickness type) reactions. The data was filled on suspected adverse drug reaction reporting form. The reactions were assessed and analyse by seriousness and outcome.

RESULTS AND DISCUSSION:

Patient demographics

During the study period, between October 2016 to April 2017, 142 snakebite victims were admitted in the government general hospital, Amravati. Among these patients, 90 (63.38%) male and 52 (36.62%) female were received ASV. Gender wise distribution of patient use of ASV is shown in figure 1. Most victims were the majority of (90) male patients as compared to female (52) patients. This can be attributed to the out-dwelling lifestyle and occupational outdoor stay of males.

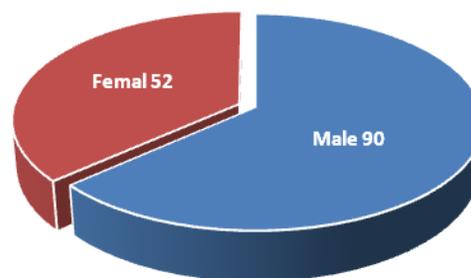


Fig 1: Gender wise distribution of patients who received ASV

Age

The age of the victims ranged from 3.5 to 80 years old. Most victims were between 21 and 30 years (35% of total patients). An incidence of snake bite was most common in age group of 21 to 30 years (35.21%), followed by 31 to 40 years (20.42%), 41 to 50 years (15.49%), 11 to 20 years (14.08%), 51 to 60 (7.74%), 61 to 70 years (4.22%), 1 to 10 years (2.12%) and 71 to 80 years (0.70%). The incidence of antivenom reactions was highest in the age group of 21-40 years (27.72%). Only three persons (8.6%) were older than 70 years. The present observation is similar to other data, for example, in a hospital based study, conducted in northern Bangladesh, the mean age was 26.7 years by Islam QT et al [9] and Devkota et al. [10] found, in Nepal, that 85% of the victims were younger than 45 years old. Thus, it was observed that snakebites occur especially among active workers. The majority of patients were farmers, plantation workers and labourers. In the present study, there was a slightly higher number of male (63.38%) than female patients (36.62%), which is not consistent with similar studies conducted in Rajshahi, Bangladesh [9], and in Nepal [10]; that found exclusively male victims outside home during working hours.

Antivenoms used, dosage forms and routes of administration

The anti-snake venom in lyophilized form used at our setup during the study duration was manufactured by, Haffkine Biopharmaceutical Company Ltd. Mumbai, VINS Bioproduct Ltd. Hyderabad and Vaccines Ltd. Mumbai. The dose of ASV largely depends upon signs of systemic envenomation and severity of bite.

In the district general hospital, Amravati, the dose of ASV was used ranges from 3 vials to 15 vials (Each vial-10 cc) depending upon signs and symptoms of the patient. Most commonly used loading dose of ASV as 10 vials (About 54.22%) followed by 5 vials dose, 3 vials dose, 15 vial doses and 8 vials dose. The ASV was diluted and infused intravenously at a constant rate over a period of about one hour.

Adverse antivenom reactions

Out of the 142 patients enrolled and used of ASV, 43 patients were suffered from ASV adverse drug reactions (ADRs). The incidence of ASV reactions was higher in male (28) patients than female (15) patients. Gender wise distribution of ASVs adverse

drug reactions (ADRs) is shown in figure 2. The incidence of ASV reactions was highest in the age group of 21 to 40 years (51.16%) followed by 41 to 60 years (25.58%), age group less than 20 years (18.6%) and age group greater than 60 years (4.65%). Only five cases required artificial ventilatory support due to respiratory muscle paralysis. The great involvement of neck muscle explained the traditional belief that there is a sequential muscle paralysis; however, this cannot be true since several muscle groups are frequently involved together [11, 12]. All enrolled patients were treated with the recommended dose of polyvalent anti-snake venom according to WHO/SEARO guidelines for the clinical management of snakebites.

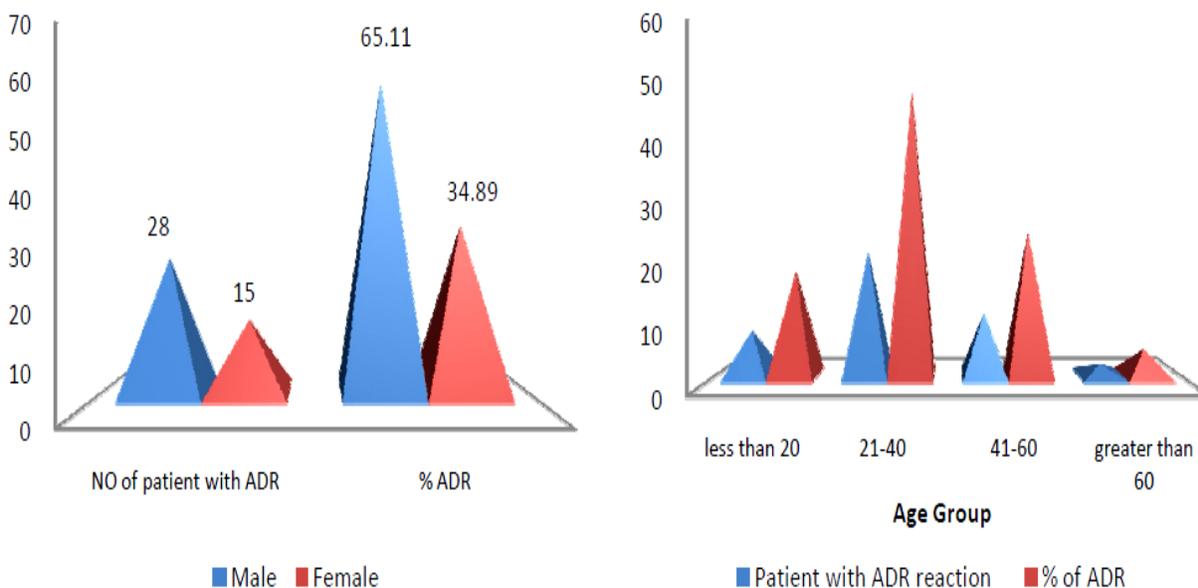


Fig 2: Gender and age wise distribution of neurotoxic snakebites for ADR

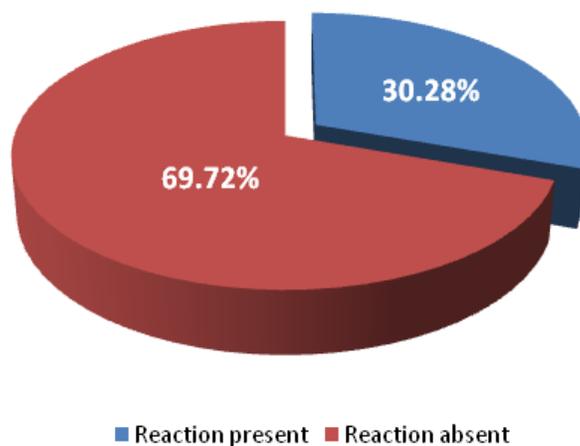


Fig 3: Distribution of adverse drug reaction of ASV

A study, accomplished in northern Bangladesh, registered seven deaths (26%) among victims treated with anti-snake venom doses ranging from 20 ml to 40 ml [9]. The most common neurological manifestation observed in snakebite victims was ptosis, in various degrees, which was found in all patients. Other signs were dysphagia, dysphonia, broken neck sign (paralysis of the cervical flexor muscles), hand-grip weakness, and depressed reflexes and generalized weakness.

Adverse antivenom reaction rates

In the current study, the total of 142 patients who have received ASV, out of them suffered 43 patients (30.28%) of snake venom reaction (figure 3). The studies were showed a higher incidence of reaction to ASV as compared to WHO literature, most of which were of early anaphylactic type or pyrogenic (endotoxic) in nature.

The most common ASV reactions were chills, rigors followed by itching, urticaria, nausea, vomiting,

hypotension and others (fever, Joint pain, Myalgia, lymphadenopathy Angioneuritic edema, tachycardia and difficulty in breathing) (figure 4). In Sri Lanka, a research found that 55.4% of patients who had received anti-snake venom were affected by adverse reactions and that there was no significant difference among reactions whether or not premedication was given [13]. The most common presentation of anaphylactic reaction in the present survey was urticaria (16 cases) that comprised 80% of all anaphylactic reactions. The investigations carried out in Sri Lankan [13] registered urticaria as a common presentation. Among ADRs patients of 43 enrolled patients, 20 developed anaphylactic reactions. Most cases presented urticaria with itching. The next common symptoms were nausea and vomiting, followed by severe anaphylaxis with wheezing and rhonchi. Only two patients developed angioedema. The other presentations were cough, headache, fever, tachycardia and palpitation.

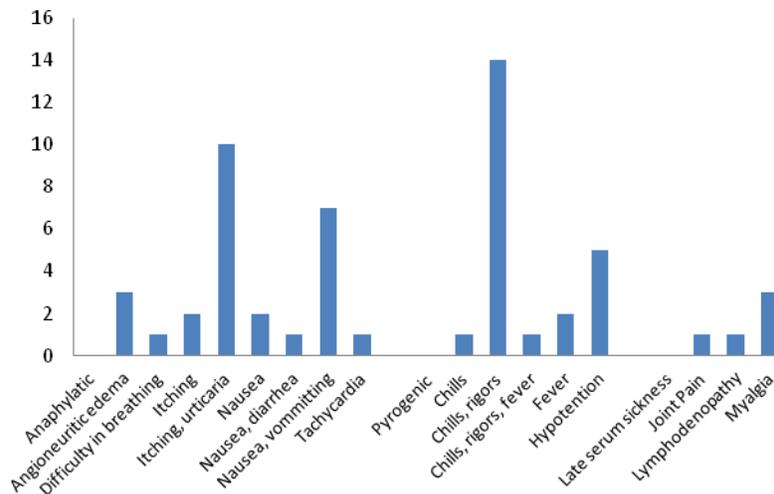


Fig 4: Adverse drug reaction of anti-snake venom

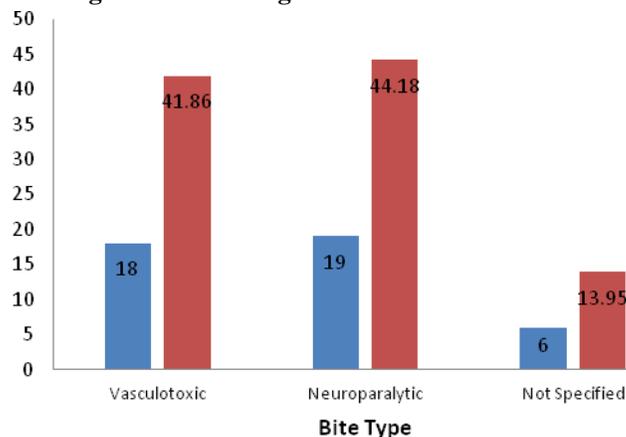


Fig 5: ADR of ASV with different type of snake-bite

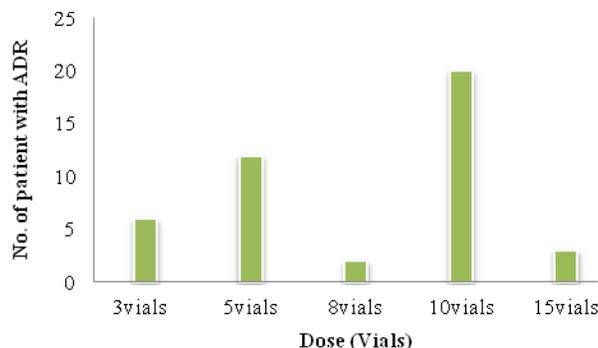


Fig 6: Dose response of ASV in term of ADRs

In current study, it was observed incidence of neuroparalytic snake bites was more than vasculotoxic snake bites and not specified snake bite. Some investigators believe that ASV reactions are seen more in vasculotoxic bites than neurotoxic ones but in our study, there was a higher incidence of ASV reactions in cases of neuroparalytic snake bites (44.18%) as compared to vasculotoxic snake bites (41.65%) (figure 5).

Dose response of ASV in term of ADRs

Incidence of ASV adverse drug reactions were more with 10 vials dose, followed by 5 vials dose, 3 vials dose, 15 vial doses and 8 vials dose.

It is found that the incidence of ASV reactions was more with dose of 10 vials (100cc) (figure 6). In the current investigation, about 82% of cases the skin hypersensitivity test was performed prior to initiation of ASV therapy. Skin testing only delays the administration of ASV and can they be sensitizing. Incidence of ASV reactions were more with dose of 10 vials (100cc) and neuroparalytic snake bites was more as compared to vasculotoxic snake bites. Anti-snake venom which is a life saving weapon is the only proven antidote but it is a double edged sword because of the allergic reactions associated with it. There was no fixed dose as individualized doses were titrated according to patient symptoms. 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 antivenom and for the treatment of antivenom-related reactions [14]. The outcome of snake bite cases is more favourable owing to the continuous and adequate supply of ASV and trained staff. There is a need of adequate documentation of adverse reactions in terms

of onset, duration, severity and outcome. Also, there is underreporting of anti-venom reactions of ASV.

CONCLUSIONS:

The antivenom is effective and specific antidote for venomous snakebites; it presents a potential risk of adverse reactions including anaphylaxis. Due to the danger of reactions the anti-snake venom should not be withheld by physicians from a snakebite victim, when indicated and appropriate guidelines should be followed for its administration. Anti-snake venom which is a life saving weapon is the only proven antidote but it is a double edged sword because of the allergic reactions associated with it. Our study showed a higher incidence of reactions to ASV at district general hospital. There is a need of adequate documentation of adverse reactions in terms of onset, duration, severity and outcome.

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Conflicts of interest

Nil.

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