Original Research Article

Role of concomitant therapy in the treatment of snakebite - A prospective, hospital based, observational study

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Abstract

Background: Snakebite is an important and serious problem in tropical and subtropical countries. In snake-bite, anti-venom is the most effective therapeutic agent available. In addition to ASV there are various other pharmacological agents like steroids, antihistamines, anticholinesterases and anti-inflammatory drugs used as supportive therapy during snake envenomation. The use of antibiotics to prevent local infection and use of steroids and antihistamines to prevent anaphylaxis is controversial. **Objectives:** The primary objective was to study the use of concomitant medications in in-patients with snake bite and the need for antibiotics and their pattern of usage. **Methodology:** This was a prospective observational study conducted on 100 patients admitted to Father Muller Medical College Hospital with a history of snakebite. Information regarding the bite and symptoms was collected from the patient. Data regarding investigations done and treatment was collected from the patient's case record file. Collected data was then analyzed. **Results:** Most of the snake bites occurred in the age group 31-45 years, 62% were males and 38% females. 82% presented to hospital within 6 hours. Reaction to ASV was the commonest complication. Premedication with antihistamine and steroid prior to ASV administration did not reduce the number of reactions (p=0.402). Penicillin was the most commonly prescribed antibiotic. Prophylactic antibiotic did not reduce the duration of stay as compared to those who did not receive antibiotics(p=0.067) The most commonly prescribed adjuvant drugs are gastroprotective agents(67%), analgesics(53%) and chymotrypsin(28%). **Conclusion:** Antibiotics were prescribed in 56, most common being penicillin. The most commonly prescribed adjuvant drugs are antacids(67%), NSAIDS(53%) and chymotrypsin(28%). Antibiotics and antihistamines needed to be given only when indicated.

Keywords: Concomitant Therapy, Snakebite, antibiotics, steroid and antihistamine

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Snakebite is a serious and important problem in tropical and subtropical countries[1] In 2007 WHO declared snakebite to be a neglected tropical disease due to the high rate of injury and death. In India, it is a major public health problem, nearly two million people fall prey to snakebite every year, resulting in 35,000 to 50,000 deaths.[2] In snake-bite, anti-venom is the most effective therapeutic agent available.[3] Rational use of anti-snake venom (ASV) neutralizes venom and helps save lives. The antivenoms are currently available against 4 most important venomous snakes. In India only polyvalent ASV is available. In

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addition to ASV there are various other pharmacological agents like steroids, antihistamines, anticholinesterases and anti-inflammatory drugs used as supportive therapy during snake envenomation. These are for the treatment of pyretic reactions, hypersensitivity to ASV, coagulopathy, neurologic complications and infections.[4] Usually more than 20% cases develop allergic reactions to ASV either early or late.[5] The use of antibiotics to prevent local infection is controversial. There is a paucity of literature regarding the drugs used in snake bite other than ASV in India. Hence the study aims to analyze the role of concomitant therapy in snakebite victims admitted to Father Muller Medical College Hospital, Mangalore, Karnataka.

MATERIALS AND METHODS

The study was a prospective observational study which was conducted on 100 patients admitted to Father Muller Medical College Hospital with a history of snakebite who met a predefined inclusion and exclusion criteria and were chosen by computer assisted random sampling. The study was initiated after obtaining an ethical clearance from the institution's ethical clearance committee. A written informed consent of the patients or from their nearest legal heir was obtained.

Inclusion Criteria:

- Patients with a history of snakebite with features of envenomation.
- Patients who have given informed consent.

Exclusion Criteria:

- Patients with a history of unknown bite.
- Patients with Diabetes mellitus.
- Patients diagnosed as HIV positive.

Information regarding the bite and symptoms was collected from the patient. Data regarding investigations done and treatment was collected from the case file. The indications, drugs used, duration of treatment and adverse reaction effects if any was documented in the proforma sheet. Patient was assessed for signs of allergy and infection. The collected data was transferred to the master chart and the data was analyzed

DATA AND STATISTICAL ANALYSIS

Demographic details of the patients were analyzed by using descriptive statistics. Continuous variables were expressed as mean and categorical variables as frequencies and percentages The collected data was analyzed using chi square test, fisher's exact test, Mann Whitney test Statistical Analysis was done using SPSS software version 23.0. A 'p' value less than 0.05($p<0.05$) is considered significant.

RESULTS AND OBSERVATIONS

In this prospective observational study conducted on 100 patients admitted to Father Muller Medical College Hospital with a history of snakebite, these were our observations. Maximum number of patients were in the age group 31 to 45 years. Males are most commonly affected (62%). The most frequent site of snakebite was the lower limb constituting 69% of bite. Most of our patients (82%) presented within 6 hours of snakebite to the hospital. Whole blood clotting test (WBCT) was found to be the most commonly deranged hematological parameter. An average of 18.28 vials of polyvalent vials of ASV per patient was administered. 11 patients developed allergic reactions to ASV. Premedication with antihistamine and steroid prior to ASV administration did not reduce the number of reactions (p=0.402) (Table 1) Antibiotics were prescribed in 56 patients, most common being penicillin. (Table 2). Prophylactic antibiotics did not reduce the duration of stay as compared to those who did not receive antibiotics(p=0.067) (Table 3). We observed the most commonly prescribed adjuvant drugs were gastroprotective agents (67%), NSAIDS (53%) and chymotrypsin (28%) (Table 4).

Table 1: COMPARISON OF ADMINISTRATION OF PREMEDICATION AND REACTIONS TO ASV

		Pheniramine maieate + hydrocortisone		Total
		0	1	
Reaction to ASV	0	27	62	89
		30.3%	69.7%	100.0%
		93.1%	87.%	89.0%
	1	2	9	11
		18.2%	81.8%	100.0%
		6.9%	12.7%	11.0%
Total		29	71	100
		29.0%	71.0%	100.0%
		100.0%	100.0%	100.0%

P=0.402, NS

Table 2: ANTIBIOTICS PRESCRIBED

ANTIBIOTIC	FREQUENCY(n)	PERCENT(%)
Penicillin	40	71.4
Metronidazole	5	8.9
Lincosamide	21	37.5
Cephalosporin	5	8.9
Total	**56**	**100**

Table 3: COMPARISON OF ADMINISTRATION OF ANTIBIOTIC and DURATION OF STAY

		No antibiotic	Prophylaxis	Total
Duration of stay	1-3	36	8	44
		81.8%	53.3%	
	4-10	6	9	12
		13.6%	40%	
	Above 10	2	1	3
		4.5%	6.66%	
Total		44	15	100
		100.0%	100.0%	100.0%

P=0.067 NS

TABLE 4: ADJUVANT DRUGS PRESCRIBED IN THIS STUDY

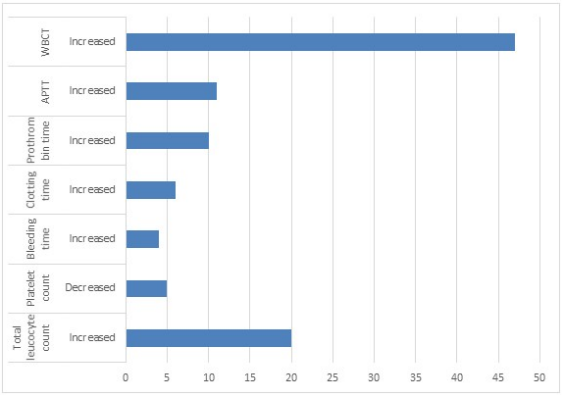
		(n)	(%)
ANALGESICS	NSAIDS	53	53
	Opioids	5	5
	NSAID + Opioid	17	17
ANTI-INFLAMMATORY	Chymotrypsin	28	28
	Serratiopeptidase	4	4
GASTROINTESTINAL DRUGS	Antiemetics	18	18
	Gastroprotective agents	67	67
VITAMINS	Vitamin b complex	19	19
	Vitamin supplement	3	3
ANTIHISTAMINE STEROID		71	71
OTHERS	Inj TT	12	12
	FFP	11	11
	Anti-anxiety	9	9

Table 5: Comparison of Gender distribution in snake bite of our study with other studies

Study	Males	Females	Ratio
Dharod MV[8]	178	103	2.4:1
Jayanta Pau[9]	127	44	2.8:1
TusharB Patil,[10]	48	9	1.5:1
Present study	62	38	1.38:1

Table 6: Comparison of age distribution in snake bite of our study with other studies

Study	Mean age in years
Dharod MV[8]	36.14
Tushar B Patil,[10]	35.77
Jayanta Paul [9]	40.47
Present study	35.61



GRAPH 1: Altered blood picture and coagulation profile of patients

DISCUSSION

Snakebite is a preventable public health hazard often faced by rural population in tropical and subtropical countries with heavy rainfall and humid climate. If diagnosis and treatment are given in a timely fashion the patients can go back to a productive life. In this prospective observational study conducted on 100 patients admitted to Father Muller Medical College Hospital with a history of snakebite, we evaluated the demographic and clinical profile, use of concomitant medications in in-patients with snake bite and the need for antibiotics and their pattern of usage.

Gender distribution in snake bite

The present study shows male preponderance (62%) similar to previous studies (Table 5). Males may be affected more as they are more actively engaged in farming and other outdoor activities.

Age distribution

Incidence of snakebite was most common in the age group of 31 to 45 yrs (33%) probably due to more ambulant nature and the fact that this age group is commonly involved in farming. Other studies also found the highest incidence among 31 to 40 yrs (27.36%) (Table 6).

Site of Bite

The most common site of bite was the lower limb (69%) as observed in other studies. (49–51%).These bites were mostly due to accidentally stepping on the snake. A total of 56 patients were brought to the hospital within 6 hours of the bite. The chief presenting symptom was local swelling and pain at the site of bite followed by bleeding. This finding was the similar to the study in Manipal.[6]

Species of snake

Species of snake was identified only in 4 cases of bite. 3 were identified to be vipers and one a common krait.

Signs of envenomation

Local signs of envenomation were seen in 59 cases, while systemic signs of envenomation were present in 41 cases. Systemic haemotoxic manifestations observed were bleeding from the site (n=31) and haematuria (n=6). Bleeding from site was the most common haemotoxic manifestation in studies done in Maharashtra[10] and Haryana.[11] Blood products like fresh frozen plasma were required by 11 cases for correction of severe coagulopathy. Blood coagulation profile is shown in Graph 1. 20min WBCT is a simple reliable test of coagulopathy.[12] WBCT was prolonged in 47% of the patients which showed the need for ASV. Constant monitoring of WBCT helps to monitor the neutralization of the venom. Monitoring of PT and PTT may give better evidence but the time taken for their normalization is long.[15] 4 patients presented with ptosis which is a sign of neurotoxic envenomation. Symptoms progressed in one of the cases leading to respiratory paralysis and required intubation. 50 vials of ASV were given to this patient over the course of stay. Atropine and neostigmine were given IV every 30 mins until the patient improved.

Reaction to ASV

ASV was given in all the cases. Test dose was not given in any. Around 5-50 vials were administered to each patient at an average of 18.28 ASV vials per patient. 11 patients developed allergic reactions to ASV. The incidence of allergic reactions was similar to those observed by others.[13,11] There were no severe anaphylactic reactions unlike the study done by Suchithra N *et al.* where eight patients had severe anaphylaxis. The most common presentation of anaphylaxis in our study was rash, breathlessness followed by chills and vomiting. In patients who developed reactions, ASV administration was temporarily discontinued, and glucocorticoid and antihistamine cover was given. Adrenaline was required in 3 patients. Once the patient recovered, ASV was restarted slowly keeping a close observation. No patient required complete stoppage of ASV due to reactions.

Mean duration of hospitalization

Mean duration of hospitalization was 4.77 days with 93% patient recovery. Mean duration was 5 days in a study done in Kerala[13] as opposed to 8 days in a study done in North India.[11]

Complications

Acute kidney injury[14] and cellulitiswere the most common complications of snake bite. Dialysis was required in 4 patients. Risk of development of acute renal failure was significant in those with higher bite to needle time.[13] Cellulitis was reported to be the most common complication by Monteiro *et al.* Cellulitis was treated with amoxicillin- clavulanate. 2 patients required fasciotomy. Soft tissue infections are a major complication. The proteolytic properties of snake venom cause tissue destruction and devitalization, which predispose the wound to bacterial infection from the snake's oral flora.[15] Although bacteria are a major cause of wound infection in snakebite patients, the role of prophylactic antibiotics to prevent the infection is debatable.[16]

Prophylaxis to prevent reaction to ASV

Prophylactic use of hydrocortisone and antihistamines before infusion of antivenom is widely implemented. Pre-medication commonly used to prevent this include glucocorticoids, chlorpheniramine and atropine.[17] In our study 71 patients were pre-medicated with injection pheniramine maleate and hydrocortisone (table number 1) prior to ASV administration. 12.7% of these patients developed a reaction to ASV as compared to 6.9% who were not premedicated. The p value is 0.402, which shows that premedication with pheniramine maleate and hydrocortisone does not help to prevent reactions to ASV. Pretreatment with hydrocortisone and/or promethazine did not reduce severe reaction rates similarly in several other studies.[18,19] This may be because hydrocortisone takes several hours to act and may be ineffective against acute adverse reactions that develop immediately after antivenom treatment. One randomized controlled trial also demonstrated no benefit from prophylaxis with IM promethazine.[20] Pre-treatment with histamine antagonists and hydrocortisone also did not prove beneficial.[21] In contrast the incidence of any grade of anaphylactic reaction was significantly lower among those who received pheniramine and hydrocortisone prophylaxis in a study by Mitra *et al.*[22]A study by Gawarammana *et al.* showed hydrocortisone alone was ineffective, but demonstrated that hydrocortisone reduces reactions when given along with chlorphenamine.[23]

Antibiotics prescribed

Antibiotics were prescribed in 56 %, 41 patients for the treatment of infection and 15 for prophylaxis. Table 2 shows the prescribing pattern of antimicrobials in our study sample. Most of the patients were prescribed a single antibiotic (n=45, 80%). 11 cases with severe infection, cellulitis/ gangrene required multiple antibiotics. The most frequently prescribed antimicrobials were penicillins (n=40) and lincosamide(n=21); followed by metronidazole(n=5) and cephalosporins(n=5). Among the penicillins, amoxicillin was the most commonly prescribed antibiotic, accounting for 28% of the prescription, followed by ampicillin and piperacillin. Commonly used combination was clindamycin with amoxicillin. The use of prophylactic antibiotics to prevent infection as a complication of local necrotic envenoming is controversial. According to Blaylock, antibiotics should be reserved for patients with necrosis and should cover Gram-negative aerobic bacilli and Gram-positive aerobic cocci.[24] It is difficult to perform bacterial culture and sensitivity for each patient. Hence regional studies are required to identify the spectrum of bacteria and their antibiotic susceptibility pattern. Staphylococcus aureus (32%) was the most common isolate followed by Escherichia coli (15%) in a study done in Pondicherry.[25] Prophylactic antibiotics did not reduce the duration of stay as compared to those who did not receive antibiotics (p=0.067). The absence of antibiotic usage in snakebite patients did not prolong hospital stay in another study.[24] Routine use of prophylactic antibiotics for pit viper envenomation also did not prevent infections.[16] Routine use of penicillin and metronidazole was not of value in reducing the local inflammatory swelling in a study done in Ceylon[26] There was no benefit of prophylactic use of antibiotics from several other reports. WHO guidelines does not recommend the prophylactic use of antibiotics as prophylactic antibiotics were not effective in a controlled study in Brazil.[27] However prophylactic course of penicillin and a single dose of broad spectrum antibiotic with a booster dose of tetanus toxoid is recommended in cases where there is a risk of wound infection.[4]

Adjuvant drugs

The most frequently prescribed adjuvant drugs other than pre-medication and antibiotics in our study sample were gastroprotective agents (n=67), NSAIDS(n=53) and chymotrypsin (n=28). Pantoprazole(n=56) and ranitidine (n=11) were commonly prescribed. These were prescribed to decrease the gastric acidity caused by the co-administered analgesics and antimicrobials. NSAIDS and chymotrypsin were prescribed to control the pain and inflammation associated with snakebite. Tetanus toxoid injection was administered in 12 cases. This is recommended if the patient has evidence of local necrosis.[28] Prophylactic premedication with IV hydrocortisone and pheniramine was given in more than 70% of patients in our study which is not concordant with standard guidelines.[6] It points to the need for continuing medical education of physicians on all aspects of treatment of snake bite. Awareness regarding this will help reduce the burden of medications taken by the patients.19 % of the patients were prescribed more than 7 drugs. There were no deaths due to snake bite during the study period. This may be due to low number of neurotoxic bites, early arrival to hospital and timely administration of antivenom. Neurotoxicity was found to be an important risk factor for mortality in patients with snake bite. Early arrival to the hospital could be one of the major causes of decreased mortality. Early reporting to the hospital may be due to the proximity of health care facilities and better roads in our area. This shows that if the victim is treated without losing too much time, mortality is potentially preventable.

CONCLUSION

In our study we came to the following conclusion;

Antihistamine and steroid use prior to ASV did not prove useful in reducing reactions to ASV. These need to be given only if the patient has a history of allergy or shows symptoms during administration of ASV. Prescribing antibiotics for prophylaxis did not help reduce the duration

of stay. Administration of snake antivenom and accessibility to hospital care within hours of the bite helps reduce mortality.

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