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Research Article

A study of outcome of neuroparalytic snake bite patients treated with fixed dose of antisnake venom

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ABSTRACT

Background: Dhule district in Maharashtra (India) has snake bite as a common medical emergency. There are 168 villages in Dhule district and its majority of the population is engaged in farming and snakebite is a major occupational hazard particularly during the harvesting season. The available data on the epidemiology of snake bite from the here is sparse. Poisonous and nonpoisonous snake bites accounts approximately 30 admissions per month which increase to 35-40 admissions in rainy season in Civil Hospital.
Methods: Fifty patients with severe neuroparalytic snake envenomation, resulting in acute type II respiratory failure, admitted to medical ICU for mechanical ventilation during one year period, were studied. Ventilatory requirements, amount of antisnake venom (ASV) infused, period of neurological recovery and hospital survival were evaluated.
Results: 60% of patients affected were in the age group of 21-40 years. Maximum numbers of bites were during April to September (84%). All patients had severe manifestations such as ptosis, ophthalmoplegia, neck muscle weakness, limb and respiratory muscle weakness. 200 ml ASV was administered to all, along with atropine and neostigmine. Mechanical ventilation was required for a median duration of 26.60 hours. All victims in the study group survived with complete neurological recovery except one mortality for a patient who had suffered irreversible hypoxic cerebral injury prior to arrival in hospital and needed ventilatory support for 9.58 days.
Conclusions: Timely institution of ventilatory support and fixed dose of 200 ml of ASV along with anticholinesterase treatment was sufficient to reverse neuroparalysis in severe elapid bites.

Keywords: Snake bite envenomation, ASV, Respiratory failure, Neuroparalysis

INTRODUCTION

World Health Organization (WHO) estimates the number of snake bites to be 83,000 per annum with 11,000 deaths.[1] In India 15000 to 20 000 people bitten by snakes die every year out of which about 2000 are from Maharashtra alone.[2] The victims of snakebites are mainly of the rural population, who are bitten during field work and when sleeping outdoors. Respiratory failure is the most important cause of morbidity and mortality in victims of neurotoxic snake bite. These patients require ventilatory assistance in addition to administration of anti-snake venom (ASV) and other supportive measures. We present our experience with management of patients with severe neuroparalytic manifestations and acute respiratory failure.

METHODS

The study was conducted in the medical intensive care unit (MICU) of Civil Hospital, Dhule, Maharashtra, India which is a tertiary care hospital affiliated to S.B.H. Govt. Medical College during the period from Jan 2012 to Dec 2012.

Inclusion criteria

- All adult (> 12 years) patients with history of neuroparalytic snake bite, who required mechanical ventilation (Table 1) for respiratory muscle paralysis, were included.

Table 1: Indications for mechanical ventilation in severe neuroparalytic snakebite.

Respiratory rate	No breathing is discernable within 10 seconds or >25-30/min
Breathing pattern	Apnea, labored and irregular pattern, agonal (gasping) breaths
Clinical signs and symptoms	Failure to cough, loss of gag reflex, Single breath count < 10/min Pooling of saliva Broken neck sign (neck muscle weakness)
ABG analysis	pH < 7.3o, paCO2>50 mmHg severe hypoxemia PaO2<60 mmHg at FiO2>50% or PaO2 < 40 mmHg at any FiO2 +
Prophylactic ventilatory support	To reduce pulmonary complications Severe cyanosis Coma

Exclusion criteria

- Snake bite victims with mild neuromuscular weakness not requiring ventilatory assistance.
- Vasculotoxic snake bites (patients with bleeding diathesis and reports showing deranged bleeding time, clotting time or decreased platelets below 100000 per microliter).
- Patients with renal failure.
- (We excluded patients with vasculotoxic snake bite as our hospital currently does not have facilities for blood products and dialysis).

Detailed history and physical examination, including the onset and nature of symptoms, site of bite, local reaction at the bite site and general and systemic manifestations, were recorded for each patient. Laboratory investigations performed at admission included haemogram and coagulogram, serum biochemistry, arterial blood gas (ABG) analysis, electrocardiogram (ECG), chest radiograph. All patients were transferred to MICU from the emergency service and ventilated using Respironics Espirit ventilators which were available in MICU. The patients were treated with lyophilized polyvalent enzyme refined equine immunoglobulins (antivenom serum; Haffkine Institute, Mumbai, India) produced against *Naja naja*, *Bangarus caeruleus*, *Vipera russelii*, and *Echis carinatus.* All patients were given tetanus toxoid. No anti-snake venom test dose was given prior to start of infusion.[3,4,5.]Based on previous evidence,[3] a dose of 10 ampoules, each reconstituted with 10 ml of diluent, and further diluted in 500 ml of isotonic saline was infused intravenously over one hour and at constant speed and patient were closely monitored. A repeat cycle of 10 ampulles of ASV was given in another one hour and then no further doses of ASV were given. Hence every ventilated patient received a total of 20 ASV ampules. Intravenous (IV) neostigmine 0.5 mg every 6 hr and IV atropine 0.5 mg diluted in infusion of 500 ml intravenous fluid over 12 hours was started. Anticholinesterase therapy was continued till the improvement of the ptosis. Initially, control mode ventilation (CMV) was used; patients were gradually switched to synchronized intermittent mandatory ventilation (SIMV) with pressure support as neuroparalysis recovered. Meticulous attention was paid to asepsis, nutrition, humidification of inspired air, regular endotracheal toileting. All patients were continuously monitored with ECG, HR, SPO2, NIBP, temperature, fluid Input /Output with ABG obtained when necessary. An effort was made to maintain oxygen fraction in inspired air (FiO2) at <0.5, while maintaining adequate oxygenation (pO2 >60 mm Hg. Weaning was accomplished by gradual reduction in the SIMV rate and the level of pressure support, once adequate respiratory effort had reappeared. A short T-piece trial was given and patients were extubated if they had normal bulbar reflexes and did not show any worsening during the period of T-piece trial.

Ultimate outcome measure studied was hospital survival. Duration of ventilation, period of neuromuscular recovery and ventilator associated complications (if any). The patients were observed for evidence of adverse effects of ASV, ventilator associated complications such as pneumonia, septicemia or barotrauma. The total dose of ASV received, the duration of ventilation with IPPV or SIMV with PSV, duration of CPAP required and T-piece ventilation and the overall outcome hours were studied. The duration of total stay in MICU and any evidence of residual neurological complications were studied. Continuous variables were compared using unpaired Student's *t* test and categorical variables using chi square test.

RESULTS

Fifty neuroparalytic snake bite patients admitted in medical ICU, having respiratory failure and on ventilatory support over a period of Jan 2012 to Dec 2012 were studied. Figure 1 shows that maximum numbers (60%) of cases were 21 to 40 years age group with male preponderance (72%) (Figure 2). Bite marks were seen in 40 (80%) and local swelling around the site of bite was present in 16 (32.4%) patients. Pain at the site of bite was present in (90.69%), burning sensation in (56.07%) and only 4.32% were having oozing from the site of bite. On local examination bite, blister formation and tissue necrosis was observed in 11.36% and 10.33% cases respectively. (Table 2). The site of bite was predominantly lower extremity (52%) followed by upper

limb (13%) (Figure 3). Hypersensitivity reaction in the form of rash 10 (20%) and brochospasm (6%) was seen in patients receiving ASV (Table 2). All the 50(100%) had severe manifestations such as ptosis, ophthalmoplegia, neck muscle weakness (broken neck sign), limb and respiratory muscle weakness. All patients in the study had evidence of type II respiratory failure as evidenced by hypercapnia ($pCO_2 > 45$ mm Hg) with or without severe hypoxaemia ($pO_2 < 60$ mm Hg) prior to intubation and ventilation. Each patient received antisnake venom in a dose of 200 ml for a median duration of 2.5 hours. 72% patients responded to neostigmine therapy (probably cobra bites) whereas 28% did not respond and neostigmine had to be discontinued (krait envenomation) (Figure 4). The mean time needed for respiratory paralysis to manifest was 12 hours. About 38 patients needed 3.5 – 14 hours to reach the hospital & mean duration of time required was 8.39 hours. The median duration of mechanical ventilation was 26.60 hours (Table 3). There was one mortality in the study group of patients. This patient had sustained irreversible neurological damage before reaching the hospital, and was ventilated for 9.58 days. However, he succumbed to complications related to aspiration pneumonia and septicaemia. In one patient with aspiration pneumonitis we had to add/change the antibiotics according to culture-sensitivity reports from endotracheal tube specimens. No patient needed reintubation in our series. All other patients improved and were discharged and had any residual neurological deficit at the time of discharge from hospital. Serum sickness was notably absent in all the 49 patients, who reported for follow up 4 weeks after discharge.

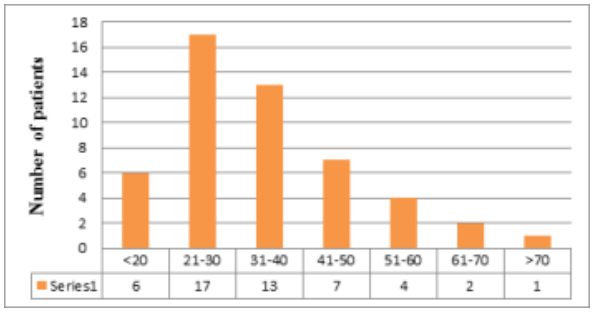

Figure 1: Age wise distribution of patients.

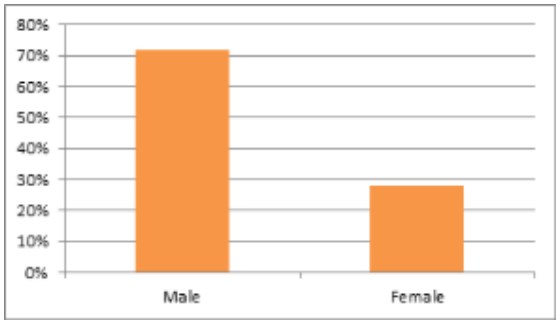

Figure 2: Sex wise distribution of snake bite patients.

Table 2: Incidence of complications by snake bite.

Nature of complication	Percentage (%)
Blister	11.36
Necrosis	10.33
Cellulitis	14.3
Bleeding/oozing	4.32
Aspiration pneumonia	2
Ventilator associated pneumonia	2
Sepsis	0
Barotrauma	0
Reintubation	0
Hypersensitivity reactions to ASV	
Rash	20
Bronchospasm	6

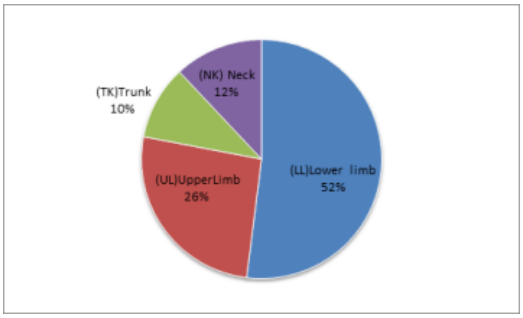

Figure 3: Bite-Injury site.

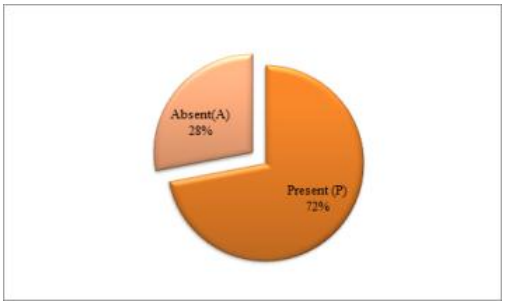

Figure 4: Response to neostigmine treatment.

Table 3

Sr. No.	Bite to Needle Time	Bite to Respiratory Failure Time	Recovery From Mechanical Ventilation	Duration of Hospital Stay (Days)
1	8	12	24	4.4
2	8.5	13	26	4.3
3	7	8.5	23	4.8
4	9	12.8	22	4.7
5	11	12.6	25	5.3
6	6	12.5	26	3.8
7	8	11	34	4.6

8	9	11.5	25	4.7
9	8.5	10.5	26	4.9
10	9.5	14	27	4.7
11	3.5	4.5	25	4.9
12	13	13	27	5.3
13	7.5	10.5	25	5.2
14	8	11.5	24.5	4.6
15	5	11	30	5.1
16	9	14.5	32	5.8
17	11	11	33	4.8
18	8	14.7	29.5	4.4
19	8.5	15	25.5	5.2
20	9	12.5	23.5	4.4
21	10	14.6	23.5	5.3
22	6	6	27	5.4
23	12	16	28	4.8
24	8.5	12.5	34	4.5
25	7	11	34	3.8
26	7.5	9	26	4.5
27	8.5	9.5	27.7	4.6
28	9.5	12	28	4.1
29	14	16	24	3.9
30	8	12	25	4.8
31	6.5	13	28	6.2
32	9.5	14.5	30	5.6
33	6.5	13.5	25	4.8
34	7.5	12.5	22.5	5.7
35	8.5	13.3	24.5	5.4
36	9.5	14.5	26	6.2
37	8.5	16.5	28	4.6
38	9.5	12.5	25.5	4.8
39	8	12.3	24	5.5
40	5	5.5	29	5.8
41	8	15.2	23.5	5.9
42	7.5	13.2	20.5	4.7
43	5	10	230*	9.58
44	4	13	26	4.9
45	8	10	25	5.2
46	7.5	11	23.5	6.4
47	8.5	15	26.5	6.3
48	2.5	9.5	28	4.8
49	3.5	7.5	28	4.2
50	5.5	13	27	4.8

DISCUSSION

The major families of poisonous snakes in India are *Elapidae*, which includes common cobra (*Najanaja*), king cobra and common krait (*B. caerulus*), viperidae includes Russell's viper, saw scaled or carpet viper (*Echis carinatus)* and pit viper and hydrophidae (sea snakes).[6] Cobra venom contains cobratoxin and α-bungarotoxin which act postsynaptically by binding to acetylcholine receptors on the motor end plate while β-bungarotoxin and crotoxin present in krait venom act presynaptically and prevent release of acetylcholine at the neuromuscular junction resulting in muscle paralysis due to curare like neuromuscular blocking action affecting the muscles of eyes, throat and chest leading to type II respiratory failure.[7,8] Respiratory failure was either a result of respiratory muscle paralysis and/or palatal paralysis leading to accumulation of secretions.

All our patients were from poor socioeconomic status from villages working in the fields and were engaged in outdoor and agricultural activitities hence prone for exposure to snakebite. Maximum numbers (68%) of cases were 21 to 40 years age group with male preponderance (72%), as was observed by (68.4%) Seneviratne U et al, [9] N. Sharma et al[10] and Kulkarni et al.[11]

70% of bites occurred during daytime (8am to 8pm) (Figure 5) and about 84% of the bites occurred during the period between May to November i.e. during summer and rainy season (Figure 6). As in most studies, the highest incidence corresponds to months of rainy season when rain water compels the snake to come out of their dwellings and agricultural activity doubles the risk of exposure. Similar climate and time preponderance were observed in studies in which 84% bites were seen in April to September by Harsoor et al, [12] which shows the influence of environmental temperatures & rain with a daytime preponderance. In our study, maximum number of bites occurred on lower extremities 52%. Limb bite constituted more than 78%, suggesting that the site of bite was predominantly determined by accidental or inadvertent contact of the snake during the farming activities. Mean time taken for the patients' arrival in hospital after the bite was 8.39 hrs in our study, which compares closely with those observed by Sharma et[10] al 8 (9 hrs) and Harssor[12] (7hrs).

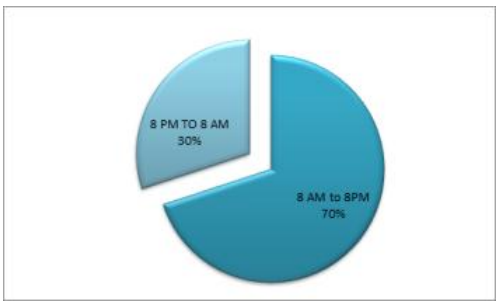

Figure 5: The time of the day of snake attack.

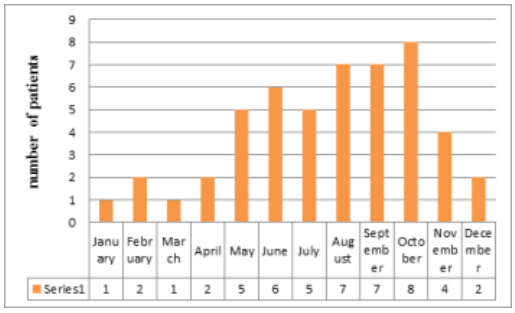

Figure 6: Monthly distribution of injuries of snakebite patients (n=50).

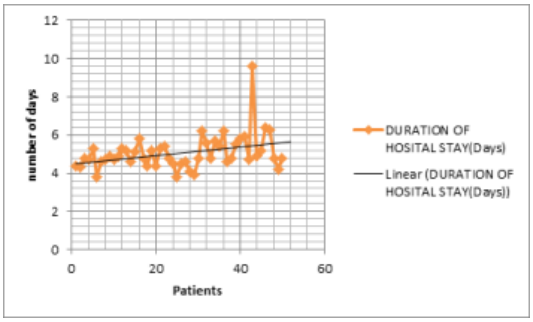

Figure 7: Duration of hospital stay.

In patients with respiratory paralysis, other clinical signs noticed were of ptosis, palatal palsy, ophthalmoplegia, pharyngeal palsy and limb and neck muscle weakness.

No test dose of ASV was given prior to infusion of ASV as WHO has recommended that intra dermal skin testing should not be used before administering ASV.[4] This test may reveal IgE mediated type 1 hyper sensitive reaction to horse protein but do not predict the large majority of early anaphylactic or late serum sickness type anti venom reactions as they are mediated by direct activation of complement system and not mediated by IgE.[15,16] Skin testing only delay the administration of ASV and can in themselves cause sensitization.

A proportion of the patients, usually more than 10%, develop a reaction either early (within a few hours) or late (five days or more) after being given the antivenom. The risk of the reactions is dose related, except in rare cases in which there had been sensitization (IgE-mediated Type I hypersensitivity) by a previous exposure to the animal serum, for example, to the equine antivenom, the tetanus-immune globulin or the rabies-immune globulin.[16] In our study, we noticed that 20% developed maculopapular rash and 6% of the patients had bronchospasm as a manifestation of allergic reactions to ASV.

ASV is the only effective and specific treatment which is available for snakebite envenomation. The anti-snake venoms may be species specific (monovalent/ monospecific) or they may be effective against several species (polyvalent/polyspecific). As per the recommendations of the WHO, the most effective treatment for snake bite is the administration of monospecific ASV; however, this therapy is not always available for the snakebite victims because of its high cost, the frequent lack of its availability, and the difficulty in correctly identifying the snake. Considering the rapid deterioration in elapid bite resulting in respiratory paralysis which is not reversible with ASV after the venom is fixed on the tissue; after the first dose of 10 vials (100 ml) of ASV a repeat dose of 100 ml of ASV was given after 1 hr of observation, if there was no improvement or deterioration in neuroparalysis.[17] If there is no improvement after 200 ml of ASV, further dose of ASV was not given and ventilation was continued till the neuromuscular recovery. The total dose given in the present study was 200 ml, which were 512 ml and 900 ml with Sharma et al.[10] and Agarwal et al[18] respectively. The total dose & the bolus dose requirement in our study is less than the recommended dose. All this patients had also received anticholinesterase (neostigmine) as also given in study by Bomb B.S. et al.[19]

Neostigmine in a dose range of 0.01-0.04 mg/kg every 1-3 h up to a maximum of 10 mg/24 h was administered by intramuscular or intravenous route. Patients were observed over 30-60 min for improved of ptosis. 72% (36) patients in our study responded to neostigmine (Figure 4) and showed improvement in ptosis and in rest of the 28% (14) patients neostigmine was discontinued in view of lack of response. Anticholinesterase drugs have a variable, but potentially useful effect in patients with neurotoxic envenoming.[18, 20] Anticholinesterases acts against the post-synaptic toxins (such as those of cobra) that induce a myasthenia-like block. They are not active against toxins acting presynaptically (common Krait). They are also not useful if administered late, as binding of toxin to acetylcholine receptors becomes relatively irreversible with time. Atropine must be given to counteract the unwanted muscarinic side effects of neostigmine, which include bradycardia, increased salivation and sweating.

Mechanical ventilation generally is safe, shorter duration and without complications in such patients, as the lungs are not diseased and have normal mechanics. Immediate endotracheal intubation is necessary for airway protection and prevention of aspiration in patients with bulbar involvement. In our study, patients after intubation were initially ventilated using Assist Control mode of ventilation. The mean duration of ventilation was 26.52 hours which was 48 hours and 82 hours respectively in studies by SAM Kularantne[20] and Harsoor[12]. In fact, our aim was to wean patients as quickly as possible because the fear of increased risk of ventilator associated pneumonia with prolonged ventilation. By employing such an early aggressive approach, we aimed to attain early recovery, improve survival and decrease the duration of mechanical ventilation, and also the incidence of associated complications.

All except one patient, in this study, had completely recovered. The only patient, who died, had sustained

irreversible hypoxic-ischemic cerebral injury because of delay in reaching the hospital. On an average, patient stayed in hospital for 5.01 days ranging from a minimum of 3.8 days to maximum of 9.58 days Table (3).

CONCLUSION

We conclude that

- Snake bite although preventable in principles, remains to be one of the common medical emergencies being more frequent in rural agricultural and farm workers.
- Most common age group affected was 21-40 years.
- Adult males are more prone to the bites in monsoon during daytime.
- Mechanical ventilatory support, along with ASV therapy, forms the backbone of management in patients with respiratory failure due to severe neuroparalytic snake envenomation.
- The strategy of giving a maximum of 200 ml of antisnake venom is as effective as using large dose ASV in severe envenomation by elapids. The ultimate outcome is excellent if therapy is administered adequately and in time. Early hospitalization and timely ASV remain the corner stones in the treatment of snakebite.
- Thus there is a need for giving health education regarding the snakebites, their toxic effects, effectiveness of hospitalization, ASV therapy in bites and prevention of snakebite by appropriate measures. This will definitely reduce the incidence and complications of snakebites.

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