

A STUDY OF COBRA ENVENOMATION: CLINICAL FEATURES AND MANAGEMENTAshish Kakaria¹, Sanjay Agarwal², Joti Bagul³**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: BACKGROUND: AIMS: To review the clinical features and management of patients with injuries related to the cobra bite. **DESIGN:** Retrospective study. **METHODS AND MATERIAL:** Patients who attended the hospital for cobra-bite related injuries from 1 April 2008 to 31 March 2009 were included. The data were obtained from the admission register, and snakebite case record sheets were then retrieved from the medical record section of hospital. Demographic data, time of occurrence, location of wound site, local and systemic complications, anti-venom therapy (number of vials), clinical outcome, any surgical intervention, and length of hospital stay were retrieved from the clinical records. **RESULTS:** Eighteen patients were recruited during the 1-year study period. Of the 18 patients with cobra bites, 14 (78 %) presented with local swelling. No patient developed severe neurotoxic symptoms. Two patients had laboratory features of haemolysis. Fourteen patients received antivenom therapy and five of them subsequently underwent surgical interventions for extensive local tissue damage and necrosis. There was no fatality. **CONCLUSION:** Bites from cobras result in serious local complications with extensive tissue necrosis and minimal neurotoxic symptoms. There is an apparent trend of favorable outcomes following the early administration of antivenom to patients without early signs of irreversible tissue damage. Ciprofloxacin should be used in infected wounds of cobra bite, if facilities for culture and sensitivity are not available.

KEYWORDS: Antivenins; Cobra venoms; Emergency treatment; Necrosis; Snake bites.

MESH TERMS: Elapidae, Cobra envenomation, snake bite.

INTRODUCTION: World Health Organization (WHO) estimates place the number of bites to be 83,000 per annum with 11,000 deaths.¹ In India 15000 people of 20 000 bitten by snakes die every year out of which about 2000 are from Maharashtra alone.² Snake bite is a common medical emergency faced mainly by rural populations in tropical and subtropical countries with heavy rainfall and humid climate. The 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 Indian subcontinent are sparse. Snake bite is a neglected disease that afflicts the most impoverished inhabitants of the rural areas in the tropical developing countries. Envenomation syndromes due to cobras in Asia vary depending on locality. Researchers reported region-specific clinical presentations due to Asiatic cobra species ranging from potentially fatal neurotoxicity but with minimal local symptoms, to extensive local tissue necrosis without neurotoxicity.

We report here the clinical presentation and management of patients with cobra related injuries seen in our institutions during the past 1 year. In particular we set out to document the liability to complications from cobra bites (including neurotoxic symptoms and local tissue necrosis) encountered locally.

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MATERIALS AND METHODS:

Design: Retrospective study.

Setting: The study was conducted in the medical wards of Civil Hospital Dhule affiliated to S.B.H. Government Medical College Dhule, Maharashtra, India.

Patients: Patients who attended the hospital for cobra-bite related injuries from 1 April 2008 to 31 March 2009 were included.

The data were obtained from the admission register, and snakebite case record sheets were then retrieved from the medical record section of hospital. The details of management were discussed with the emergency doctors and staff involved in the management of snakebite.

Data were analyzed for clinico-epidemiological profile, and for each incident, demographic data, time of occurrence and location of wound site, local and systemic complications, antivenom therapy (number of vials), clinical outcome, any surgical intervention, length of hospital stay were retrieved from the clinical records. Main outcome measures were injured category, venom characteristics, response to treatment, extent of the damage, the nature of injuries, envenoming features, complications, response to antivenom therapy, and outcome.

Statistical Methods: The data obtained was analyzed by descriptive statistics by means of percentage, proportions and depicted via bar charts.

RESULTS: During the study period, there were a total of 18 confirmed cases of cobra related injuries. For six incidents, the dead snake specimen was available for identification. Ten patients were able to identify the snakes to be cobra clearly, using the snake photo handbook. Two others were bitten by snakes of similar appearance and developed typical clinical features of cobra-bite poisoning. On the other hand, four patients with suspected cobra injuries were excluded, because their wounds lacked typical clinical features, despite the cobras having been described or identified by the respective patients.

Time of occurrence and wound site of snake Bite: Among the confirmed cases, 18 incidents, 14 (78%) occurred in the summer and monsoon period (between April and November), 13 (72%) ensued in the daytime (06:00-17:59), and eight (44%) occurred indoors. Most of the cobra bites involved the lower limbs (Table 1). All but two patients arrived at the hospital within 2 hours of presentation.

According to month of the year	Patients (n)
January	0
February	0
March	1
April	1
May	1
June	0
July	1

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August	6
September	2
October	4
November	2
December	0
According to time of injury	
0000-0559	1
0600-1159	5
1200-1759	8
1800-2359	4
According to body part involved	
Upper limb	4
Lower limb	14
According to location	
Indoors	8
Outdoors	10

Table1: Patients presenting with cobra bites

Local and systemic complications from cobra Bites: Eleven of the 18 patients with cobra bites complained of paraesthesia over the wounds and in three of them, paraesthesias progressed over the entire forearm although the bite was on the fingers and thumb. No patient developed severe neurotoxic symptoms (limb weakness, respiratory muscle paralysis, or apnoea), but on presentation two had gastro-intestinal symptoms (including nausea and vomiting).

Of the 18 patients, 14 presented with swelling over bitten areas (Table 2), around half of whom (6/14) developed necrosis over the injured area and five were treated by debridement (Table 3). Three patients treated by debridement received a skin graft or skin flap for wound repair due to the extensive area involved.

Two patients developed laboratory features of haemolysis with a reduction in haemoglobin (Hb) level, elevated blood bilirubin and lactate dehydrogenase (LDH) levels. One patient developed a coagulopathy associated with the wound infection. Electrocardiograms (ECG) performed on 13 patients revealed no obvious abnormalities. Moreover, none of the 15 patients developed cardiovascular instability (hypotension or bradycardia), and there was no mortality.

Patient (n)	Sex/age (years)	Location of bite	Bite-to needle time (hours)	Nervous symptoms‡	Local symptom§
Without surgical intervention					
1*	M/34	Right ankle	3	+	P, E
2	F/44	Right little finger	3	++	-
3	F/44	Left foot	4	+	S, E
4	F/44	Right thumb	6	++	P, E

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5	M/51	Right thumb	3	++	P, E
6	F/67	Right thumb	3	+	S, E
7	F/20	Left 5th toe	7	+	S, E
8	M/44	Right 3rd toe	12	+	S, E
9	M/48	Right thumb	2	-	S, E
10	F/9	Left foot	4	-	P, E
With surgical intervention					
11	F/78	Right 4th toe	2	-	S, E
12	M/58	Left ankle	25	-	P, E
13	F/26	Left 5th toe	1	+	S, E
14	F/24	Right leg	2	+	S, B
15†	M/59	Left 5th toe	-	+	S, B, N

Table 2: Features of patients with Cobra Envenomation

* This patient was discharged against medical advice and the outcome was unknown

† No antivenoms therapy because of delayed presentation

‡ Neurotoxicity: + = paraesthesia over bitten area, ++ = progressive paraesthesia of the affected limb.

§ Extension of swelling: P = pain without obvious swelling, S = extensive swelling well beyond the bitten area; local skin condition: E = erythema, B = bruising or discoloration of skin; N = necrosis.

Case No.	Operations	Extension of necrosis (depth)	Length of stay (days)
11	Repeated debridement x 3 + skin graft	3rd, 4th and 5th toe, to lateral Malleolus (subcutaneous tissue)	3+22*
12	Debridement + skin flap and graft	Anterolateral aspect of distal 1/3 of leg to lateral dorsum of foot (subcutaneous tissue)	31
13	Repeated debridement x 2+ skin graft	Extended to dorsum of foot (subcutaneous tissue)	29
14	Bedside debridement under local anaesthesia x 4	Lateral aspect of foot (subcutaneous tissue)	6+7+64*

Table 3: Details pertaining to patients having surgical interventions

* Repeated admission for wound care.

† Debridement on follow-up.

Antivenom therapy and clinical Outcome: 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*. No anti-snake venom test dose was given prior to start of infusion.^{3,4,5}

Fourteen of the 15 patients with cobra bites were given antivenom. Local pain and swelling were the indications we adopted for antivenom in 13 patients.

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The remaining patient (case 2) had progressive paraesthesia over her injured limb; her symptoms improved soon after the administration of antivenom. The median time lag to antivenom administration after the snakebites was 3 hours (range, 1-25 hours). Treatment was discontinued once there was cessation of progressive swelling or neurotoxic symptoms. The number of vials given ranged from 1 to 21. In our patients, no allergic reaction or adverse effect was encountered after using antivenom. All patients with cobra bites were frequently reassessed (every 2 to 4 hours).

The decision to administer additional antivenom doses was made by individual physicians, based on the perceived clinical response to treatment. The timing of repeated antivenom doses ranged from 2 to 12 hours, depending on the perceived progress of symptoms and availability of antivenom. Patients who recovered without tissue necrosis received at least two vials of antivenom. For patient 6 with a cobra bite over her right thumb and progressive swelling across the wrist, 21 vials of antivenom were used in total. The local swelling subsequently subsided, and was followed by only a small area of necrosis, which healed without surgical interventions.

The outcome of patient 1 was unknown, as he was discharged against medical advice. Five patients developed extensive tissue necrosis treated by surgical interventions. Among these, patient 15 did not receive antivenom due to delayed presentation (22 hours post-injury) and tissue necrosis at presentation. The other four each received 1 to 18 vials of antivenom therapy (Table 3). In patient 12, administration of antivenom was delayed due to difficulty in snake identification.

Further enquiries about the snake's appearance and review of the clinical features confirmed the cobra bite. The first dose of antivenom was therefore given 25 hours post-injury. Although the swelling ceased progressing after 12 vials of antivenom, the local skin condition deteriorated and extensive tissue necrosis ensued, despite administration of a total of 18 vials. Patients 11, 13, and 14 developed extensive tissue necrosis for which surgical interventions were carried out, although their antivenom therapy was started within 4 hours of injury (Tables 2 and 3).

Patient 11 had cobra bite over her right fourth toe and was admitted into medical ward for further management after one vial of antivenom given in the AED. There was no obvious progression of swelling during her stay in medical ward. She was subsequently discharged on day 3. However, extensive swelling was noticed when the patient was followed up in the outpatient clinic on day 10 post-injury. She was admitted into the orthopaedic ward for further management. Patient 13 presented with a cobra bite on her left little toe.

The contents of two vials of antivenom were given about 1 hour after envenomation. The patient had progressive pain and swelling across her left ankle during reassessment. Another six vials of antivenom were used 13 hours post-injury, but with no improvement. Subsequently, skin necrosis developed despite a total of 20 vials antivenom being used. Patient 14 presented with swelling and dark discoloration of the wound 1 hour after a cobra bite over her left ankle.

A total of six vials of antivenom were given. Despite the apparent cessation of the progression of swelling, blisters formed that were subsequently followed by ulceration and necrosis, for which repeated surgical debridement was performed. Very likely due to her prolonged immobilization, she stayed in the orthopedic ward for around 2 months for rehabilitation.

Length of Stay: Most of the patients with cobra bites (11/15) had short hospital stays (1-4 days). Four patients (6, 12, 13, and 14) had repeated admissions or a prolonged stay for wound care (Table 3).

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DISCUSSION: The major families of poisonous snakes in India are Cobrae, which includes common cobra (*Naja naja*), king cobra and common krait (*B. caeruleus*), 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 pre-synaptically 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 respiratory failure.^{2,3,4}

All our patients were from poor socioeconomic status from villages that work in the fields, stay in the huts & sleep on the open floor and hence more are prone for snake bites. 90% of them were above 10 years of age with female (64%) preponderance, whereas male dominance was observed by Seneviratne U et al,⁷ N. Sharma et al⁸ and Kulkarni et al.⁹ 18 incidents, 14(78%) occurred in the summer and early autumn period (between August and November), 13(72%) ensued in the daytime (06:00-17:59), and eight (44%) occurred indoors.

Climate and time preponderance was also observed in studies by Harsoor et al,¹⁰ which showed the influence of environmental temperatures and rain with midnight preponderance. Severity of envenomation and progression to respiratory failure is related to several factors such as dose of venom injected (which depends on the mechanical efficiency of bite species and size of snake, condition of fangs, and whether the snake has recently fed or is injured), potency of venom (which depends on species, age and health of snake), anatomic location of bite (whether proximal or distal), age, health, size and possibly immune status of victim, and the nature and timing of first-aid and medical treatment.¹¹ In all such patients, timely administration of ASV and institution of cardiorespiratory support is associated with an excellent outcome.^{11,12}

Time of Occurrence: The seasonal distribution (mainly in summer and early autumn) of cobra-related injuries in our study had a similar pattern to that described in a previous local epidemiological study on snake bites.⁶ The cobras are active day and night. However, the majority of incidents in our series happened during daylight. Their bites in general cause local and neurological complications, but difference in venom composition accounts for geographical variations in clinical features following cobra bites. Apparently, bites from the same cobra species in different regions may also present differently.¹³

Neurotoxicity: The neurotoxin (the primary lethal component in cobra venom) blocks acetylcholine receptors in the postsynaptic regions of motor end plates without affecting the release of acetylcholine in presynaptic terminals. Phospholipase A₂ in cobra venom was shown to have additional neuromuscular blocking activity *in vitro*.¹⁴ Antivenom therapy and respiratory support is the mainstay for treating neuromuscular paralysis. In addition, neostigmine has been successfully used to overcome neuromuscular blockade after Asiatic cobra bites.^{15,16,17}

The clinical manifestations of neurotoxicity include: ptosis, ophthalmoplegia, dysphagia, flaccid paralysis, respiratory paralysis, and coma. A study from Wanje and Gadekar¹⁸ on cobra bites reported neurotoxicity with muscle weakness in 15% (4/27) of the patients. However, in our series profound neurotoxicity after bites by cobra was not encountered.

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Haemolysis: Studies have demonstrated that the venom from cobra has significant hemolytic activity, including a synergistic effect of the cardiotoxin with phospholipidase A₂. An in-vitro study revealed that the cardiotoxin from cobra venom caused disintegration of the membrane structure of human erythrocytes, which potentiates the hydrolysis of phospholipids in the membrane by the phospholipase A₂. Cases of haemolysis, with a 7.32 ± 1.38 g/L decrease of Hb level, in patients with snake bite has been reported by Kale.¹⁹ In our study, patients 12 and 18 developed features of haemolysis with decreases in Hb concentration (by 2.5 and 5 g/L, respectively), and increases of both bilirubin and LDH levels.

Local tissue Necrosis: Cobra venoms cause extensive local tissue destruction, mainly due to the effect of cytotoxins and myotoxic phospholipase A₂, while the local effects from viper bites are mainly due to haemorrhagic metalloproteinases, which are also responsible for the haemorrhagic syndrome after such envenomation. Metalloproteinase has not been identified in the cobra venom. Animal studies show that tissue damage occurs as early as 5 minutes after intradermal injection of phospholipase A₂.

Histopathological study on cobra bite wounds in humans revealed focal necrosis within the epidermis with thrombosis and fibrinoid deposits in the superficial and deep dermal vessels, as well as features of leukocytoclastic vasculitis. The extensive local tissue damage from cobra venom is believed to result from the direct cytotoxic effects, with ischaemia secondary to vascular change of the dermal vessels and subsequent bacterial infection.¹⁹

Extensive areas of dark discoloration over the wounds in our patients probably indicate local tissue ischaemia that could be an early sign of irreversible tissue damage. In contrast to viper bites that cause deep tissue damage, local tissue damage due to cobra bites is generally superficial and limited to the skin and subcutaneous tissue. Our series demonstrated that cobra envenomation caused necrosis involving skin and subcutaneous tissue, with sparing of the muscle layer.

The depth and extension of tissue involvement probably depend on the depth to which venom is injected. The cobra has short fangs so that the venom is injected in the subcutaneous layer and rarely causes extensive muscle damage.

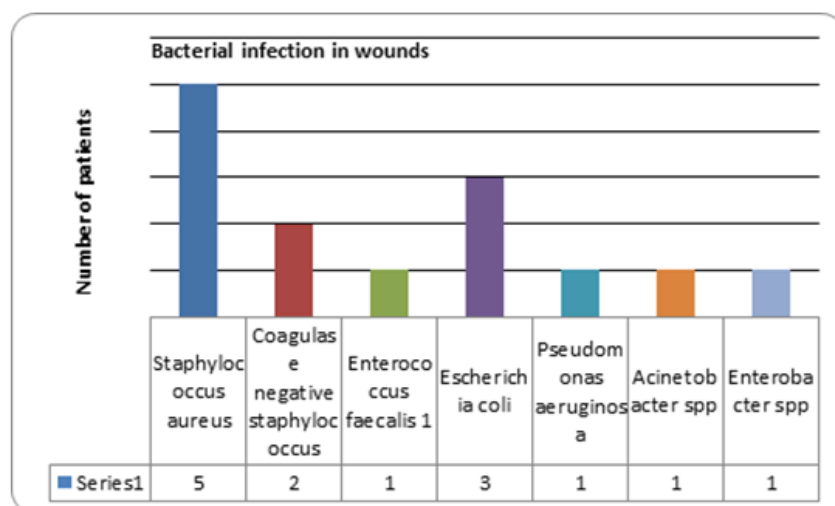


Fig. 1: Bacterial growth in wound (n=14)

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Bacterial Infection: Five patients presented with subcutaneous abscess and 2 had localized tissue necrosis. Monomicrobial infection was seen in 82% cases whereas 18% had mixed infection. Gram positive bacteria were isolated more frequently (57.14%) than Gram negative bacteria (42.86%). (Figure 1) A study from Garg et al²⁰ showed *Staphylococcus aureus* (32%) was the most common isolate followed by *Escherichia coli* (15%); monomicrobial infections were more frequent than polymicrobial infections. The majority of the isolates were antibiotic sensitive. Ciprofloxacin, an oral drug covering both Gram-positive and Gram-negative isolates, was the most frequently prescribed antibiotic.

We look forward to a further study focusing on early use of antivenom after cobra bites, to evaluate possible improvement at the site of injury, minimization of tissue necrosis, and avoidance of destructive surgical interventions. This strategy appears justified, as none of our patients developed anaphylaxis or delayed serum sickness even after very large doses (up to 21vials), and according to other local experience with snake antivenom, allergic reactions are uncommon.

Although early signs of skin necrosis—skin discoloration and blister formation—developed in the first 3 days after envenomation in most of the patients, delayed necrosis also seemed to occur (patient 11). Follow-up assessment is needed after 1 week, even if the progression of swelling appears well-controlled following initial antivenom therapy.

CONCLUSION: Envenoming by cobra may cause serious local complications. Early use of antivenom after cobra bites leads to minimization of tissue necrosis, and avoidance of destructive surgical interventions. There is a trend towards better local outcomes associated with early antivenom use (within 12 hours). It is difficult to perform bacterial culture and antimicrobial susceptibility for every patient of snakebite particularly for those living in rural and tribal areas; Ciprofloxacin use is effective in patients who develop wound infection secondary to snakebite in countries in Southeast Asia.

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