SSR Institute of International Journal of Life Sciences
ISSN (O): 2581-8740 | ISSN (P): 2581-8732
Mallick *et al*., 2024
DOI: 10.21276/SSR-IIJLS.2024.10.2.31

Research Article

open access

Electrophysiologic Evaluation of Snake Bite: A Comparative Study

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Received: 08 Nov 2023/ Revised: 09 Dec 2023/ Accepted: 10 Feb 2024

ABSTRACT

Background: Snake venoms cause human toxicity in the nervous, cardiovascular, and hematological systems. Recent data challenges traditional toxicity concepts and highlights the diverse nature of snake toxins. Therefore, this study aims to compare electrophysiological responses of snake bites.

Methods: The study involved 50 patients with a history of neurotoxic snake bites, both male and female, who underwent nerve conduction studies. The study used standard machine equipment, temperature control, distance measurements, and recording of responses. Motor nerve conduction and repetitive nerve stimulation were performed on median and facial nerves using surface electrodes. The amplitude, latency, and velocity of conduction in the nerves were recorded.

Results: It is evident that third, fourth, and sixth cranial nerves were commonly involved after neurotoxic snake bite of which third cranial nerve is the commonest and which is predominantly found in krait bite. Ptosis is present in all cases of krait and cobra bites. 18 cases presented with opthalmoplegia, out of which 41% are krait bite and 18.2% are cobra bite. Facial muscle weakness was observed in 84% of cases, with 87.2% being krait bites and 72.7% being cobra bites. The pharyngeal reflex was diminished in 89.7% of krait bites and 72.7% in cobra bites. Neck muscle weakness was observed in 16 cases, with 38.5% being krait bites and 9.0% being cobra bites. Most cases required neostigmine therapy for 48-72 hours.

Conclusion: The study confirms that early morning flaccid paralysis with ptosis, despite no snake bite history, requires early treatment with ASV and anticholinesterase for neurotoxic snake bites.

Key-words: Acetylcholine, Anticholinesterase, Neurotoxicity, Snake bite, Snake venom

INTRODUCTION

The fear of snakes is a strong, ancient, and potentially natural human emotion that has captivated evolutionists and experimental psychologists [1]. Farmers and farm laborers are susceptible to envenomation by venomous creatures, such as wasps, spiders, ants, scorpions, and snakes [2]. Acute flaccid paralysis is frequently caused by snakebite, which is also the primary cause of mortality for young, well-off family members [3]. Snakebite is considered a neglected tropical illness by the WHO [4,5] because of the extent of its impact and the scarcity of resources in tropical and subtropical areas.

Snake venoms that impact the neurological system (neurotoxic), the cardiovascular system (cardiotoxic), or the hematological system (hemotoxic/vasculotoxic) can all be harmful to humans. Recent research shows the wide variety of snake toxins and casts doubt on conventional theories of toxicity in snake envenomation. It is currently acknowledged that among all natural poisons, snake venoms are the most complicated [6].

A complex cocktail of enzymes, polypeptides, nonenzymatic proteins, nucleotides, and other chemicals, many of which may have distinct neurotoxic qualities, makes up snake venom rather than a homogenous single toxin. The following are some instances of the diversity of toxins found in different types of snakes: Cobra *Naja* sp. (alpha-cobratoxin, cobrotoxin, cardiotoxin, toxin alpha,

How to cite this article
Mallick SK, Pradhan PK, Panda CD. Electrophysiologic Evaluation of Snake Bite: A Comparative Study. SSR Inst Int J Life Sci., 2024; 10(2): 5222-5228.

Access this article online
https://iijls.com/

DOI: 10.21276/SSR-IIJLS.2024.10.2.31

weak toxin); Krait, *Bungarus* sp. (alpha-bungarotoxin, beta-bungarotoxin, kappa bungarotoxin, candoxin); Russell's viper, *Daboia* sp. (phospholipase A2 activity, daboia neurotoxin-1, viperotoxin-F); Mamba, *Dendroa* sp. (dendrotoxins, fasciculins, muscarinic toxins, calciseptine); Rattlesnake, *Crotalus* sp. (Crotoxin, Mojave toxin) [7].

A malfunctioning neuromuscular junction (NMJ) transmission causes the peripheral neuromuscular paralysis that follows a snakebite. Presynaptic and postsynaptic neuromuscular blockade have historically been thought to be the two types of neuromuscular blockade caused by snake venom toxins; however, this theory may be oversimplistic and needs to be reviewed in light of recent discoveries regarding neuromuscular transmission and descriptions of various patterns of neurotoxicity [8]. Even vipers, which are typically regarded as "vasculotoxic snakes," have a considerable risk of producing neurological poisoning. At first, it was believed that these vasculotoxic snakes only indirectly affected the vasculature of the central and peripheral nerve systems to cause neurological toxicity [9]. Now, however, it is known that these snakes directly cause neuromuscular poisoning. The site of action of the venom determines the clinical manifestations of the patients. The clinical response of the patient is typically used to guide the management of envenomation from a snake bite. A thorough neurophysiological investigation may offer an unbiased evaluation of the degree of neuroparalytic disease and the efficacy of the treatment regimen.

MATERIALS AND METHODS

This was a comparative and observational study conducted at SCB Medical College and Hospital, Cuttack for over one year.

Inclusion criteria- All cases of neurotoxic snake bite patients of age 14 and above admitted in SCB MCH with normal 20-minute WBCT and bleeding manifestation and patients who have given informed consent were included in the study.

Exclusion criteria- Non-venomous snakebite and venomous snakebites with no neurological manifestations, pregnant women and persons with any co-existing illness, snakebite cases with neurological manifestation but with abnormal 20-minute WBCT and snakebite cases with known neurological disease were excluded from the study.

Methodology- A minimum 50 patients both male and female with a history of neurotoxic snake bite with neurological manifestations admitted to SCB MCH were studied. The offending snakes were identified either by examination (where the snake was killed and brought to the hospital) or based on eyewitness accounts. Besides when there is an unknown snake bite or unknown bite patients with neurotoxic manifestation with local sign were considered as cobra bite and neurotoxic manifestation without local sign was considered a krait bite. Complete clinical history and thorough clinical examination of the patient with snake bite were done. 20 minutes WBCT will be done. Anti-snake venom injection was administered as per the National Guidelines. 0.5 ml of neostigmine was given intravenously and they reviewed in 10 minutes, 20 minutes, 30 minutes and the degree of ptosis and muscle power was studied. 5 ml of blood was kept at -20^{0}C for further study. Ambulatory patients underwent the electrophysiological test.

Electrophysiological evaluation of peripheral nerve function- Studies on nerve conduction were performed on the patients. The Department of Medicine's standard RMS ALERON 401 machine was used to measure nerve conduction characteristics. The normal protocol was followed during recording, which included maintaining a temperature between 32 and 34^{o}C, taking precise measurements of distance, and recording responses that were distinct and devoid of artifacts.

Both sides' median and facial nerves were subjected to motor nerve conduction and repeated nerve stimulation (RNS). Surface electrodes were used during the process. The motor action potential's amplitude, latency, and conduction velocity in the relevant nerve were measured. Following this motor nerve conduction, a study involving repeated nerve stimulation (RNS) was conducted. In this case, the face and median nerves were used for RNS.

The nerve was repeatedly stimulated in this investigation, either at 5 cycles per second (slow RNS) or 30 cycles per second (fast RNS), with 5–100 stimuli delivered. To determine whether a decrement was

DOI: 10.21276/SSR-IIJLS.2024.10.2.31

present, the action potentials that resulted from this repetitive stimulation were sequentially recorded. The amplitude of the first (s1) and fourth (s4) action potentials were compared. If the test's results were indeterminate, it was

repeated after 30 seconds of voluntary muscle contraction. If this was not possible (for patients in a comatose state), the test was repeated after the muscle was repeatedly stimulated to promote voluntary muscle contraction. This document served as the study's post-tetanic action potential. According to the usual procedure, a decrement was deemed significant if it was greater than 10% (i.e. a decrement of 10%) for s4/s1, which is the amplitude difference between the fourth and first stimuli during the repeated stimulation investigation. When testing at 30 cycles per second, a 20% or greater decline was deemed noteworthy.

Statistical analysis- The statistical analysis of the gathered data was conducted with SPSS 25.0. The significance level for categorical data was set at a probability value of 0.05, and the Chi-Square test was employed to identify significance.

Ethical approval- Before the commencement of the study, ethical approval was obtained from the institutional review board or ethics committee.

RESULTS

The site of the bite was the lower extremities in a maximum number of patients (56%). Out of these, krait bite (53.8%) and cobra bite (63.6%) occurred in the lower limbs. The significant number of krait bites (35.9%) in the upper limb. Krait bites can be found all over the body parts including the back, head and neck, trunk as most of the bites occur during sleep hours inside the house but cobra bite is predominantly found in the upper and lower extremities as farmers and labourer working in the field (Table 1).

Table 1: Site of different snake bites in patients.

Site	Krait (%)	Cobra (%)	No. of cases (%)	p-value
Leg	21(53.8)	7(63.6)	28(56)	0.86
Hand	14(35.9)	4(36.4)	18(36)	
Back	1(2.6)	0(0)	1(2)	
Head & Neck	2(5.1)	0(0)	2(4)	
Trunk	1(2.6)	0(0)	1(2)	
Total	39	11	50	

Table 2 shows that in most of the cases, the symptoms appeared after 1-4 hrs of snake bite with a mean delay of 2.56±0.09 hrs. The maximum delay in onset of symptoms in this study was 6 hrs, which was a case of suspected krait bite. In the majority of cobra bite (72.7%) and krait bite (76.9%) the onset of the first symptom occurred within 4 hrs.

Table 2: Onset of the first symptom after bite.

Time	Krait (%)	Cobra (%)	No. of cases (%)
<1hr	5(12.8)	0(0)	5(10)
1-4hr	30(76.9)	8(72.7)	38(76)
>4hrs	4(10.2)	3(27.3)	7(14)
Total	39	11	50
Mean±SD	2.46±0.11hrs	3±0.53hrs	p-value = 0.23

The most common presentation was drooping of the eyelid which was present in all patients (100%). The second most common presentation was dysphagia or difficulty in swallowing (86%). Slurring of speech (70%) and dyspnea (82%) were significantly present in the patients (Table 3).

DOI: 10.21276/SSR-IIJLS.2024.10.2.31

Table 3: Spectrum of clinical presentation after neurotoxic snake bite.

Symptoms	Krait (%) (n=39)	Cobra (%) (n=11)	Total (%) (n=50)	p-value
Local swelling	0(0)	11(100)	15(30)	<0.001
Dysphagia	34(87.18)	9(81.82)	43(86)	0.964
Dyspnea	32(82.05)	9(81.82)	41(82)	0.669
Slurring of speech	26(66.67)	9(81.82)	35(70)	0.582
Double vision	14(35.90)	2(18.18)	16(32)	0.455
Drooping of eyelid	39(100)	11(100)	50(100)	0.864
Weakness of limbs	16(41.03)	4(36.36)	20(40)	0.943
Pain abomen	2(5.13)	1(9.09)	3(6.0)	0.694

The most common physical findings following neurotoxic snake bite was ptosis (100%) followed by weakness of pharyngeal reflex (86%), among 97.4% are of krait bite and weakness of facial nerve (84%) then muscle tenderness is highest among the cobra bite (90.9%). Diminished deep tendon reflex was found in 41.1% of krait bite and 9.0% among cobra bite cases. There was no sensory deficit and extensor planter response seen in both krait and cobra bite. 17.9% of krait bites and 27.2% of cobra bites are presented with altered sensorium, this may be due to administration of atropine along with neostigmine (Table 4).

Table 4: Physical findings in patients with neurotoxic snakebite (n=50).

Findings	Krait (%) (n=39)	Cobra (%) (n=11)	No. of Cases (%)
Tachycardia	2(5.1)	0(0)	2(4)
Hypotension	0(0)	0(0)	0(0)
Ptosis	39(100)	11(100)	50(100)
Altered mental status	7(17.9)	3(27.2)	10(20)
Opthalmoplegia	16(41.0)	2(18.2)	18(36)
Weakness of facial nerve	34(87.2)	8(72.7)	42(84)
Weakness of pharyngeal reflex	38(97.4)	5(45.5)	43(86)
Weakness of neck muscle	15(38.4)	1(9.0)	16(32)
Muscle tenderness	22(54.4)	10(90.9)	32(64)
Quadriparesis	16(41.0)	4 (36.4)	20(40)
Diminished deep tendon Reflex (DTR)	18(41.1)	1(9.0)	19(38)
Sensory deficit	0(0)	0(0)	0(0)
Extension planter response	0(0)	0(0)	0(0)
Total	39	11	50

From Table 5 it is evident that the third, fourth, and sixth cranial nerves were commonly involved after neurotoxic snake bites of which the third cranial nerve is the commonest and which is predominantly found in krait bites. Ptosis is present in all cases of krait and cobra bites. 18 cases presented with ophthalmoplegia, out of which 41% are krait bite and 18.2% are cobra bite.

Facial muscle weakness is found in 84% of cases, among which 87.2% are krait bite and 72.7% are cobra bite. An almost equal number of cases i.e., 89.7% in krait bite and 72.7% in cobra bite developed diminished pharyngeal reflex. 16 cases developed weakness of neck muscle, out of which 38.5% are krait bites and 9.0% are cobra bites.

DOI: 10.21276/SSR-IIJLS.2024.10.2.31

Table 5: Incidence of CN palsy in neurotoxic snake bite.

CN palsy	Krait (%) (n=39)	Cobra (%) (n=11)	No. of cases (%) (n=50)
III, IV, VI Ptosis Opthalmoplegia	 39(100) 16(41.0)	 11(100) 02(18.2)	 50(100) 18(36)
V- Weakness of muscles of mastication	35(89.7)	9(81.8)	44(88.0)
VII- Facial muscle weakness	34(87.2)	08(72.7)	42(84)
IX, X, XI, XII Decrease pharyngeal reflex Weakness of neck muscle	 35(89.7) 15(38.5)	 08(72.7) 01(9.0)	 43(86) 16(32)

Table 6 shows that a majority (60%) of cases required neostigmine therapy for 48-72 hrs. Out of 30 cases that required neostigmine therapy for 72 hrs, 23 cases were krait and 7 cases were cobra. None of the cases received neostigmine therapy for less than 24 hrs. Only one krait bite was given neostigmine therapy for 96 hrs.

Table 6: Duration of neostigmine therapy in neurotoxic snake bite (n=50).

Duration	Krait (%) (n=39)	Cobra (%) (n=11)	Total (%)
<12hrs	0(0)	0(0)	0(0)
12-24hrs	0(0)	0(0)	0(0)
24-48hrs	15(38.5)	4(36.4)	19(38)
48-72hrs	23(59)	7(63.6)	30(60)
72-96hrs	01(2.5)	0(0)	1(2)
Mean±SD	7.8±10.6	2.2±3.1	p=0.85

The present study also showed that the majority of snake bites (80%) required 20 vials of ASV, among which krait bite (89.7%) and cobra bite (45.5%). 05 cases (10%) required 10 vials of ASV and 30 vials of ASV. None of the cases required more than 30 vials of ASV. PT/INR ratio was found normal in all cases of neurotoxic snake bite. It is also evident that all cases of cobra bites have abnormal serum CPK levels while 25 cases (64.1%) of krait bites have normal serum CPK levels. Around equal no of cases of neurotoxic snake bites has serum CPK level 121-500U/L. 54.5% cases of cobra bite and 7.7% cases of krait have serum CPK level 501-1000U/L. Only 2 cases have serum CPK level>1000.

DISCUSSION

In the neurophysiological studies conducted on these patients, three patterns of neuromuscular transmission failures were noted [10]: postsynaptic reversible neuromuscular blockade (Cobra spp. *Naja-naja, Naja-nigricollis, Naja-haje*); postsynaptic irreversible blockade-alpha-bungarotoxin; presynaptic blockade with inhibition of release of acetylcholine-Beta- and gamma-bungarotoxin, phospholipase A2 activity, viperotoxin F.

While a decremental response at low-frequency repetitive nerve stimulation (RNS) is suggestive of a postsynaptic neuromuscular blockade, low-amplitude compound muscle action potentials (CMAPs) are representative of a presynaptic disorder of neuromuscular transmission [11]. Observation of fibrillation potentials in the electromyographic evaluation may also support a presynaptic site of action [12].

There is a paucity of human data regarding the neurophysiological alterations following a snake bite. Furthermore, because different researchers have used different methods (e.g., different sample sizes, different rates of repetitive stimulation, time of study after a snake bite, and specifications of treatment modalities used while undergoing neurophysiological examination), it is challenging to interpret the results of these studies.

A reduction in the amplitudes of CMAPs and a decrease in the response to 3 Hz RNS were the two relevant

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neurophysiological abnormalities that Singh *et al.* observed in their investigation of twelve individuals infected with B. caeruleus [13]. The degree of neuromuscular paralysis and the clinical findings showed a strong link with the neurophysiological abnormalities, they also observed. It was deduced by them that pre- and post-synaptic blockage at the NMJ causes the neuromuscular symptoms of a snake bite [14].

Reduced CMAP, post-activation potentiation, and a decremental response on 5 Hz RNS were seen in a study of three subjects envenomed by the Papuan taipan snake (Oxyuranus scutellatus canni). This investigation also found that blocking on single-fiber electromyography enhanced jitter. A likely presynaptic location for neuromuscular inhibition was proposed [15]. In two individuals who had been poisoned by a Philippine cobra, Watt *et al.* observed a decreasing reaction at 5 Hz RNS. They proposed that the etiology in their patients was a postsynaptic neuromuscular blockage [16]. Seneviratne and Dissanayake tested eight of their patients who had been bitten by snakes using the edrophonium method. A good reaction was shown by seven patients. Three patients had kraits as the offending snakes, two had Rusell vipers, and two had unknown snakes. It was believed that the blockage at the postsynaptic NMJ was the cause of the positive edrophonium response observed in these patients [17].

Patwari *et al.* investigated the electrophysiological profile of 40 patients bitten by a snake. They examined the electrophysiology of neurotoxic and vasculotoxic snake bites individually and found no notable abnormalities or statistically significant differences in amplitude, distal latency, and conduction velocities in any group [18]. In the RNS investigation, they observed a decrease in response at 3 Hz (with significant postexercise reduction) in either group in both the median and face nerves. Even patients bitten by vasculotoxic snakes experienced significant electrophysiological changes despite the absence of neurological symptoms [19].

Establishing suitable care regimens for snake bite envenomation patients may be aided by thorough neurophysiological research, particularly in cases when the clinical presentation is non-classical. It's important to remember that even vipers, which are typically categorized as "vasculotoxic snakes," have a considerable risk of producing neurological toxicity.

Studies on the neurophysiological assessment of snake bites are scarce, despite the high incidence of snake bites in the Indian subcontinent. A thorough and impartial model of the kind and extent of neurological dysfunction would be provided by research aimed at assessing the neurophysiological effects of snake envenomation. The clinical decision-making process for these patients would be substantially aided by additional research on these facets of snake envenomation.

CONCLUSIONS

The results of EMG and NCV tests were all normal reports on days 3-5 of admission in both cobra and krait bites. The majority of patients recovered within 3 days. So this suggests snake bite neurotoxicity is reversible without residual paralysis. The motor and sensory nerve conduction were normal in all cases. There was no abnormality in the amplitude and configuration of CAMP and SNAP. This confirms that the venom has no action on the peripheral nerve. The present study confirms that acute onset flaccid paralysis occurring in the early morning hours with ptosis even in the absence of any snake bite history or local signs of snake bite needs to be treated as due to neurotoxic snake bite. Early administration of ASV along with anticholinesterase can save the life of neurotoxic snake bites. Future studies could focus on standardizing methods for neurophysiological examinations post-snake bites to improve result interpretation.

CONTRIBUTION OF AUTHORS

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Supervision- Pradyut Kumar Pradhan

Materials- Chinmaya Debasis Panda, Subarna Kumar Mallick

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Data analysis and Interpretation- Chinmaya Debasis Panda

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DOI: 10.21276/SSR-IIJLS.2024.10.2.31

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