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Clinical profile and outcome of patients of common krait bite with features of neurotoxic envenomation, treated with intravenous calcium gluconate infusion in conjunction with AVS, a tertiary care center-based study

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ABSTRACT

Background: Snake bite is one of the most neglected diseases in South East Asian region. Common Krait (CK) (*Bungarus caeruleus*) is the deadliest snake found in the dry zones of India. With the polyvalent anti-venom serum (AVS) remaining the cornerstone of treatment of neurotoxic snake envenomation, there is no universally accepted treatment for CK envenomation-associated neuroparalysis, except supportive measures. **Aims and Objectives:** Our study was conducted to describe the epidemiology, define clinical features, study outcome, and apparent efficacy of calcium gluconate in preventing or reversing neuromuscular paralysis with respiratory failure in CK bite patients. **Materials and Methods**: This study is a prospective observational study done on 52 CK bite patients. Patients were enrolled according to inclusion and exclusion criteria and were treated with AVS and calcium gluconate infusion according to National Standard Guideline, 2016. Patients developing severe respiratory muscle paralysis were offered mechanical ventilation. **Results:** Patients developed ptosis and dysphagia, pain abdomen, cyanosis, paralysis of jaw and tongue, perioral numbness, altered sensorium, dysphonia, ophthalmoplegia, and paradoxical breathing. 21.15% of patients developed respiratory failure and needed ventilator support with average critical care unit stay of 3 days and average stay on a ventilator of 2 days. 3 patients expired (case fatality rate 5.77%). The average hospital stay was 3.33 days. **Conclusion**: Our study shows that early intervention in patients of CK bite with neurotoxic envenomation, with calcium gluconate infusion, leads to less mortality and morbidity compared to other relevant studies. Further large-scale studies are required for better understanding and implementation.

Key words: Common krait; Neuroparalysis; Calcium gluconate; Neurotoxic snake envenomation; Anti-venom serum

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INTRODUCTION

Ophitoxaemia (snake envenomation) is a common acute life-threatening medical emergency. World health organization (WHO) described this health hazard as a neglected disease in South East Asian region.[1] It is a preventable public health hazard often faced by the rural population in tropical and subtropical countries with heavy rainfall and humid climate. There are more than 2000 species of snakes in the world and about 216 species of snakes identifiable in India. Fortunately, only a few of them are known to be of medical importance. The major

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families of poisonous snakes in India are Elapidae and Viperidae. Elapidae includes the common cobra (*Naja naja*), king cobra and common krait (CK) which are generally neurotoxic. Viperidae includes Russell's viper, sawscaled or carpet viper and pit viper, which are vasculotoxic. Hydrophidae (sea snakes) are myotoxic.[2] Worldwide about 1.2 million–5.5 million cases of snake bite occur and about 20–94 thousand estimated deaths occur because of these reptile bites.[3] In India, only 7.23% of cases of snake bite-related deaths get reported, as many victims go to traditional healers and many deaths occur before reaching the hospital.[4] Survey of 1.1 million homes was conducted in 2001–2003. The study found 562 deaths (0.47% of total deaths) were assigned to snakebites, mostly in rural areas, and more common among males. A retrospective study, conducted in Maharashtra, showed that the annual incidence of snakebite was 36/100,000 population with a case fatality rate of 4.5%.

The CK (*Bungarus caeruleus*) is a proteroglyphous elapid snake commonly found in rural areas of India, Sri Lanka, Pakistan, and Bangladesh. The maximum number of krait bites occurs in the states of Uttar Pradesh, Andhra Pradesh, Bihar, Tamil Nadu, West Bengal, Maharashtra, and Kerala.[4] A significant number of krait bite victims die before reaching hospital. A study done by Majumder et al., showed that almost 67% of all the snake bites deaths occurred due to bite of CK, most of them occurring from June to September.[5] However, in recent years, the case fatality rate has reduced due to improved awareness, better transportation facilities, prompt therapy with polyvalent anti-venom serum (AVS), and availability of assisted ventilation modalities.

Till date, there is no effective treatment of CK bite with features of neurotoxic envenomation except AVS infusion. Neostigmine therapy consists of the initial management in snake bites with signs of neurological deficit, but CK bites usually do not respond to anticholinesterase. In national STG, 2016 provision of Calcium gluconate infusion has been kept after failure of atropine neostigmine trial in neurotoxic snake bite.[4] Furthermore, in the snakebite management protocol of West Bengal, there is mention to use calcium gluconate in patients with presynaptic neurotoxic snake bite with features of envenomation (CK bites).[6] However, there is a variable opinion regarding the efficacy of calcium gluconate therapy in neurotoxic envenomation among the treating physicians. Some studies have also shown that calcium gluconate has no role in Cobra bite-associated neuroparalysis.

The aim of the study was to describe the epidemiology, define clinical features, study outcome, and apparent efficacy of calcium gluconate in preventing or reversing neuromuscular paralysis with respiratory failure in CK bite patients.

Aims and objectives

Our study was conducted to describe the epidemiology, define clinical features, study outcome and apparent efficacy of calcium gluconate in preventing of reversing neuromuscular paralysis with respiratory failure in comm9n krait bite patients.

MATERIALS AND METHODS

It is a prospective observational study. The study was conducted on 52 CK bite patients admitted to the in-patient department of Internal Medicine and critical care unit (CCU), Bankura Sammilani Medical College and Hospital. All the patients admitted with CK bite with features of neurotoxic envenomation, from January 1st, 2022, to November 30th, 2022, were included in the study by complete enumeration method. The patients were included with a history of snake bite with either studying the brought dead snake or showing patients specimens of formalin preserved snakes, and/or clinical features of CK bite. 20 min whole blood clotting test was done and if the result remained negative then injection neostigmine 1.5 mg I.M./I.V. with injection atropine 0.6 mg I.V. stat dose was given. Then injection neostigmine (0.5 mg) with injection atropine (0.6) mg was repeated twice at an interval of 30 min. If there was no response in the form of improvement of ptosis or improvement of ptosis <50%, then the patient was diagnosed as a case of CK bite and was included in our study. Patients with neurotoxic snake bites where significant improvement (improvement of ptosis ≥50%) was observed with 3 doses of neostigmine or patients whose legally acceptable representatives had denied giving consent for inclusion in the study or patients with a history or sign of prior neurological dysfunction, were excluded from the study. Clinical features of CK bite include very fine bite marks or no bite mark at all, ptosis, inability to maintain upward gaze, diplopia, or ophthalmoplegia, paralysis of jaw and tongue, pain abdomen, numbness around the lips and mouth, cyanosis, altered sensorium and/or paradoxical breathing. Clinical assessment included examination of eye movements, pupillary size and reaction to light, power of neck flexors and limb muscles, intrapalpebral distance, respiratory rate and pattern, tidal volume, chest expansion, speech, level of consciousness, brain stem reflexes, cardiac status and improvement of ptosis. Further assessment included complete blood count, blood urea and BUN, serum creatinine, arterial blood gas, serum pH, and 12 lead electrocardiogram. There was regular follow-up of the survivors participating in the study.

The routine management protocol of CK bite in our hospital was adopted according to national STG, 2016 without any modification.[4] Initial resuscitation was the

cornerstone of management and patients with established or impending respiratory paralysis were offered assisted ventilation. Patients with stable respiration were screened and monitored for early neuromuscular respiratory paralysis. All the patients received initial 10 vials of AVS and the dose was repeated after 1–2 h in case of refractory neuroparalysis and/or persistent pain abdomen. Vital parameters such as heart rate and rhythm, peripheral oxygen saturation, maintenance of fluid balance, physiotherapy, adjustment of assisted ventilation to maintain normal blood gasses, early detection, and treatment of complications either by a result of envenoming or mechanical ventilation were closely monitored. Details including age, sex, socioeconomic status, time, place and site of bite, and clinical assessment, investigations, complications, outcome, and treatment were documented in a well-designed proforma. Recovered patients were followed up for late sequalae.

The data were compiled into Microsoft excel sheet and for data analysis software packages like Statistical Package for Social Science (SPSS-22.0 trial version, Armonk, NY; IBM Corp) were used.

RESULTS

A total of 52 patients of CK bite with a definite feature of envenomation were included in the study.

Sociodemographic status, time of bite, and seasonal distribution

Most of the patients were from poor farming families living in villages in and near Bankura, Burdwan, and Midnapore districts. Among the 52 patients, 19 (36.5%) were <25 years old, 24 (46.1%) were 25–50 years old, and 9 (17.4%) were in the age group of more than 50 years. Among the 52 patients, 29 (56%) were male and 23 (44%) were female.

17 (32%) of the snake bite victims had Krait bite over their lower limbs, 25 (48.1%) had bite over other areas of the body, mostly prevalent over arms, hands, back, and occasionally over ear lobules and scalp. 10 (19.2%) patients neither could isolate the site or bite nor had any bite mark. These patients were presented with two different scenarios. One category came up with complaint sight of a snake in the vicinity, but no discernible bite history. The other category presented with severe pain abdomen in the morning with other features of neurotoxicity, likely to be bitten at night, while asleep.

21 (40%) patients suffered Krait bite in daylight, while 31 (60%) patients either had a history of or were suspected of snake bite at night.

The maximum number of Krait bites [36 (68.94%)] occurred during the rainy seasons, especially in June to August, and the number receded to become nil in the winter (Figure 1).

Clinical profile

26 (50%) of patients suffering from diagnosed or suspected CK bite did not have any bite mark over their body. The rest 26 (50%) had some bite marks over the area concerned. No local swelling, pain, numbness, necrosis, blistering, or gangrene were observed during the hospital stay.

Among the patients of CK bite, most patients developed ptosis (98.1%) and dysphagia (98.1%), followed by pain abdomen (96.2%). Cyanosis was the least common among the patients (only 5.8% of patients developed this sign). Other clinical features in decreasing prevalence are paralysis of jaw and tongue (55.8%), perioral numbness (40.4%), altered sensorium (34.7%), dysphonia (19.2%), diplopia/ophthalmoplegia, and paradoxical breathing (both being 15.4%) (Table 1).

44 (84.6% of the total study population) received 20 vials of AVS. 2 (3.9%) received 10 vials of AVS. 6 (11.5%) received more than 20 vials of AVS. The average number of AVS used per patient suffering from krait bite is 21 vials.

Among the patients who developed pain abdomen, 26 of them were relieved from the symptom on the 1st day, 19 on the 2nd day, and 3 on the 3rd day, whereas 2 of them expired without resolution of the pain abdomen. Furthermore, among the patients who developed dysphagia, 28 were relieved on the 1st day, 14 on the 2nd day, 6 on the 3rd day, and 1 expired without resolution of the symptom (Figure 2).

Among the patients who developed ptosis, the symptom resolved within 2–5 days (mode 3 days). Three patients died without resolution of ptosis.

A total of 11 patients developed respiratory paralysis and needed mechanical ventilator support in CCU. The average days of CCU stay by patients with respiratory failure is 3 days and average days on ventilator is 2 days (Table 2).

The average hospital stay of total krait bite patients was 3.33 days. Among the patients who did not develop respiratory muscle paralysis, it was 3.14 days. Among the CCU admitted patients, average hospital stay was 4.04 days.

DISCUSSION

Snake bite is an acute medical emergency which is described by WHO as one the most neglected disease in the South East Asian region. The species *B. caeruleus* (CK) is an elapid snake commonly found in the states of India, Sri Lanka, Pakistan, and Bangladesh. Common victims of krait bite are people from farming families or people living in clay

Table 1: Distribution of study population according to clinical features at admission and during hospital stay (n=52)

Clinical feature	Number of patients	Percentage
Ptosis	51	98.1
Diplopia/ophthalmoplegia	8	15.4
Paralysis of jaw or tongue	29	55.8
Pain abdomen	50	96.2
Perioral numbness	21	40.4
Cyanosis	3	5.8
Altered sensorium	18	34.7
Paradoxical breathing	8	15.4
Dysphagia	51	98.1
Dysphonia	10	19.2

Table 2: Number of days each patient has stayed in CCU among the patients who developed acute respiratory muscle paralysis (n=11)

Patient serial no	Days in CCU	Days on ventilator
Patient 1	4	Expired
Patient 2	3	2
Patient 3	5	3
Patient 4	1	Expired
Patient 5	5	4
Patient 6	4	1
Patient 7	1	1
Patient 8	3	2
Patient 9	2	1
Patient 10	3	2
Patient 11	1	Expired
Average	3	2

CCC: Critical care unit

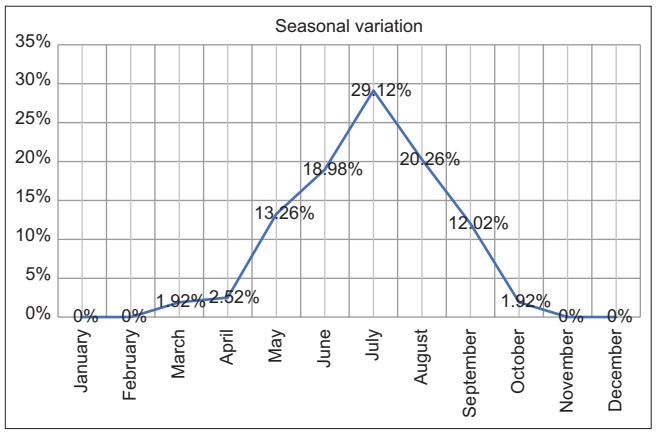

Figure 1: Distribution of study population according to the month of bite (n=52)

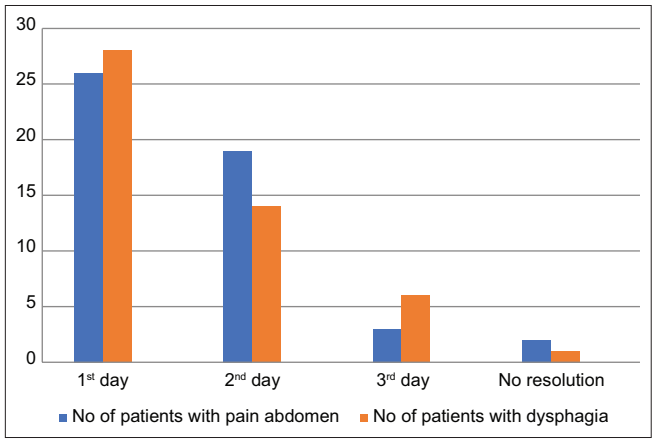

Figure 2: Number of days required by patients suffering from krait bite for resolution of pain abdomen and dysphagia

huts, wattle-and-daub houses where individuals tend to sleep on the floor. CK possesses beta-bungarotoxin, acting on synaptic vesicular proteins and voltage-gated calcium channels at the neuromuscular junction, ultimately blocking the neuro-transmission and leading to neuromuscular paralysis. The mortality rate was 77% in a study done in India on 35 proved CK bites who received only traditional treatment with polyvalent AVS.[7] Some studies done in Sri Lanka indicated that 97% of snake bites deaths in the country occurred attributed to CK and Russell's viper bites. There is no authentic study done in India concluding the incidence, percentage, or clinical profile of krait bite patients in India.

The incidence of snakebites depends on the frequency of contact between snakes and human. Snakes are usually elusive and reclusive creatures. Snakebites occur when people get near the habitat of snakes such as paddy fields, tea, rubber, and coffee plantations, bushes for open field latrine, and besides the water bodies during fishing. Bites may be inflicted at home by peri-domestic species which lives in roof space or under floor like cobras and CK. The seasonal peak of snakebite is noted in the summer and rainy seasons. Increase in agricultural activity or heavy rain leading to flooding of the natural habitats of snakes increase the chance of snake-human contact. During flood, there may be epidemic of snakebites. Males are bitten more than females as outdoor activity after sunset is predominantly done by males. The peak age of bite is 15–45 years.

The most common cause of death in neurotoxic snake bite is bulbar and respiratory paralysis. The only effective treatment for respiratory muscle paralysis is mechanical ventilation in a CCU setup. However, CCU setup is not readily available everywhere in a developing country like India, especially in the rural health setups. Mechanical ventilation also has its own complication apart from the psychosocial trauma and morbidity associated with it, most predominantly in the elderly age groups.

The CK is a nocturnal, terrestrial predator which lives close to human dwellings, though this is timid in nature. It creeps into houses through holes in the ground or from roof and exhibits arboreal tendencies. A study was done in Sri Lanka in 1998, on 210 patients of CK bite.[8] The study

concluded that most bite occurred at night, mostly when the victims were asleep. Our study also testifies the fact with 60% of bites being at night. The krait feeds on mice, rats, and geckos which are abundant in rural houses. The snake, being attracted by these prey, creeps into houses. While asleep, humans may roll over or startle the snake, or exposed part of the human body might be misidentified as prey. These factors may be the causes of nocturnal krait bites, despite of the snake being naturally indolent. Environmental factors like rain influence the mobilization of snakes from their natural habitats leading to more incidences of snake bites.

General signs and symptoms of neurotoxic envenomation

- Progressive paralysis, initially of bulbar muscles (muscles supplied by cranial nerves), starting with ptosis, difficulty in maintaining upward gaze, double vision, or ophthalmoplegia. The patient complains of a feeling of heaviness over his/her eyelids[6]
- Perioral numbness and dysphagia
- Paralysis of jaw and tongue may lead to upper airway obstruction. Pharyngeal palsy may cause impaired swallowing, leading to pooled secretions in the oral cavity. Aspiration of pooled secretion may complicate the case consequently
- Epigastric pain suggesting submucosal hemorrhage in the stomach (krait bite) [earliest presentation]. When a patient is unaware of the bite, he usually wakes up 2–4 h after the bite, due to severe colicky pain, mainly in the epigastrium. This symptom can be misdiagnosed as acute abdomen unless high suspicion is adopted by a medical practitioner
- Krait bites are often present in the early morning with paralysis that can be mistaken as a stroke
- Early morning pain abdomen is the commonest presentation in krait bite
- Respiratory muscle paralysis may lead to hypoxia due to inadequate ventilation, cyanosis, altered sensorium, and coma. This is a life-threatening situation and needs urgent assisted mechanical ventilation
- Paradoxical breathing, as a result of diaphragmatic palsy and paralysis of intercostal muscles, is a frequent sign
- Neuroparalytic snakebite patients present with typical symptoms within 30 mins-2 h in case of cobra bite and 3–24 h for krait bite; however, ptosis in krait bite has been recorded as late as 36 h after an incident of bite
- Other rare symptoms include chest pain, giddiness, myalgia, vomiting, and blurred vision.

The polyvalent AVS is prepared from horse serum against 4 species of snakes commonly founf in India, (1) Indian Spectacle Cobra, (2) Russell's Viper, (3) CK, (4) Sawscaled Viper. The polyvalent AVS has doubtful efficacy in reversing established neuromuscular blockade. Even though it can neutralize the unbound venom in the circulation, it has no effect on bound antigen in neuromuscular junctions, which can occur very rapidly post-envenomation. Whatsoever, the role of AVS can not be overemphasized in preventing impending neuroparalysis and respiratory failure.

Diagnosis and management of krait bite

All the patients with both krait and cobra bite initially presented with similar features of neuroparalysis. Once the patient is suspected to develop signs and symptoms of neurotoxicity, 1.5 mg of IM/IV neostigmine is administered, along with 0.6 mg of IV atropine and 10 vials of AVS infusion. Then the patient is observed for 30 min. If there is an improvement of ptosis of more than or equal to 50% in the period, then it is suspected to be a case of Cobra bite and 0.5 mg of neostigmine is repeated for 5 times in 30 min intervals. If there is no or <50% improvement of ptosis after 3 doses of neostigmine or there is worsening of signs and symptoms, a second dose of 1.5 mg of neostigmine and 0.6 mg of atropine is repeated along with 10 more vials of AVS infusion. If ptosis still does not improve by >50%, then it is probably a case of krait bite. Then, injection calcium gluconate 10ml IV (1:1 dilution) is infused slowly over 5-10 min every 6 hourly till neuroparalysis recovers (which may last for 6–7 days).[4]

Dr. Sreedevi, Dr. P.V.V. Satyanarayana et el. Conducted a case study where a 15-years-old male patient with features of neurotoxic snake bite was given AN trial with the administration of AVS. He was observed for 1 h and no response to AN trial could be elicited. Calcium Gluconate 10 cc was given in IV infusion over 10 min and repeated every 6 hourly. 50% improvement in ptosis after the second dose was observed and complete recovery occurred on 3rd day, and weaned off from the ventilator on the 4th day.[9]

A study was done by Kularatne S, on 210 patients of krait bite with features of systemic envenomation. Despite treating all the patients with conventional AVS infusion, 101 (48.1%) of them were put on mechanical ventilation support. Duration of ventilation ranged from 12 h to 29 days (mode 2 days).[8] Overall mortality rate was 7.6%, despite early intervention.

In our study, among the 52 patients, 11 (21.15%) developed respiratory failure and needed emergency or elective mechanical ventilator support in CCU. The average days of CCU stay by patients with respiratory failure is 3 days and average days on ventilator is 2 days. 3 patients expired with the mortality rate being (5.77%). Average hospital stay of krait bite patients was 3.33 days. Among the patients

who did not develop respiratory muscle paralysis, it was 3.14 days. Among the CCU-admitted patients, the average hospital stay was 4.04 days.

Limitations of the study

This is a small study done in three districts of South-West part of West Bengal. Versatility of krait venoms all over the world and inclusion of patients suffering from krait envenomation from this small geographic area poses as a major limitation of this study. The study population was small, attributed by short duration of the study.

CONCLUSION

There is variable opinion regarding the efficacy of calcium gluconate in neurotoxic snake envenomation to manage presynaptic block of neurotransmitters, respiratory muscle paralysis, and their consequences. The WHO has not mentioned calcium gluconate as essential to treat neurotoxicity in CK bite in the standard treatment protocol for snake bite management guidelines due to the paucity of data. National STG 2016 and training module for management of snake bite and common poisons (the protocol used in West Bengal) has however demonstrated calcium gluconate for specific patients.[4,6] There is no large-scale study in India showing the efficacy of calcium gluconate in neurotoxic snake bite with presynaptic block. Our study shows that early intervention in patients of CK bite with neurotoxic envenomation, with calcium gluconate infusion, leads to less respiratory failure with mechanical ventilation compared to the study done in Sri Lanka (21.12% vs. 48.1%).[8] This is a small study done in South-East part of West Bengal, India. Further studies are required to be done to look for the biological plausibility of calcium gluconate's mechanism of action in presynaptic snake bite envenomation, and also if the therapy should be adopted as a universal protocol.

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ETHICAL APPROVAL

Permission from the Institutional Ethics Committee of our institution was obtained before data collection.

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Authors' Contributions:
SM- Definition of intellectual content, literature survey. prepared first draft of manuscript, implementation of study protocol; **SG** and **NS**- Review manuscript; **SJM**- Literature survey and preparation of figures; **AC and TC:** Coordination and manuscript revision; **SD**- Concept, literature survey, design, clinical protocol, data collection, data analysis, manuscript preparation, editing, manuscript revision, submission of article.

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