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Role of neostigmine and polyvalent antivenom in Indian common krait (*Bungarus caeruleus*) bite

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Summary *Bungarus caeruleus* (Indian common krait) bite during monsoons is common in Northwest India. This study was undertaken to find the effectiveness of neostigmine and polyvalent antivenom in improving neuromuscular paralysis following bite. All the consecutive patients admitted between June 2007 and December 2008 with common krait bite, identified either from brought snake or circumstantial evidence were studied. Ten vials of polyvalent antivenom and three doses of 2.5 mg neostigmine at 30 min intervals after administration of 0.6 mg of atropine were administered I.V. and patients were assessed for any improvement in neuroparalysis. Seventy-two patients were admitted during the study period. All the patients except two came from rural areas and were brought between June and September. Sixty-two patients were bitten during the day while clearing bricks, cutting grass or walking. The mean time interval between bite and arrival to hospital was 4.5 h. None of the patients showed any improvement following treatment and all patients developed respiratory paralysis, requiring assisted ventilation. Seventy survived and two died. Neostigmine is ineffective in reversing or improving neuroparalytic features in patients with *B. caeruleus* bite even at higher dose than normally recommended.

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Introduction

The common krait (*Bungarus caeruleus*) is the most toxic snake found commonly in the plains of Northwest India and bites typically occur during July—September [1—3]. Kraits are elapid snakes and within the single genus *Bungarus*, 12 species are found [4]. They are generally nocturnal, shy and non-aggressive. Their diet consists of other snakes and it will therefore pursue them into human habitation, where the prey species are hunting for rodents. Bites generally occur when kraits are disturbed by sleeping humans moving, either naturally, or during REM sleep [5]. A significant number of patients die before they reach the hospital, largely due to the fact that the bite does not inflict sufficient pain or as a result of the bite itself or venom action and the victims are therefore unaware that they have been bitten.

In reported outcomes in proven common krait bites from Northwest India, mortality has been as high as 77% [6]. However since the availability of assisted ventilation, mortality is considerably lower in those patients who reach hospital in time.

The role of anticholinesterases in reversing neuroparalysis is controversial [5,7—12]. Kularatne et al. from Sri Lanka reported the failure of anticholinesterases and polyvalent antivenom in reversing paralysis or reducing duration of ventilation in 210 patients (99 with the identified snake) bitten by common krait (*B. caeruleus*) [5]. In Malayan krait (*Bungarus candidus*), one patient was reported as responding to neostigmine [7]. Anticholinesterase drugs, e.g. neostigmine, if proven effective in improving response to pre-synaptic envenomings such as krait bites, they can potentially present a significant intervention in improving patient outcome. Available polyvalent anti-snake venom (ASV) in India are only in lyophilized form and takes 30—60 min to be reconstituted. If anticholinestrase drugs are proven to be effective they could be deployed more rapidly and may improve patient outcome.

The present study was undertaken to establish the profile of venomous snake bite victims admitted in our hospital. We documented clinical features, outcome, efficacy of polyvalent antivenom and anticholinesterase, i.e. neostigmine in reversing neuroparalysis. As well to define optimum intensive care management of common krait envenoming bite.

Patients and methods

This study was carried out over a period of 18 months from late June 2007 to 31 December 2008. All the consecutive patients with confirmed envenoming admitted to the emergency ward of Nehru Hospital attached to the Postgraduate Institute of Medical Education and Research, Chandigarh, a tertiary care referral center in Northwest India, were included in this study.

The details of age, sex, socioeconomic status, time, place and site of bite, clinical assessment, investigations and treatment were all recorded on proforma developed by the National Snakebite Committee in 2006 at the National Snakebite Meeting in Kochi (India). Patients were identified as having been bitten by common krait either by studying the characteristics of the snake, where the dead snake was produced, or identifying the snake from morphological description provided by patient and by showing them formalin preserved snakes. If it was still not possible to confirm the species, clinical features and circumstantial evidence were employed to identify the snake. The dead snakes brought by patients/attendants were preserved in 10% formalin and identified by an experienced herpetologist, using standard morphological keys (IDS).

Patients were assessed at the time of admission and then periodically until final outcome. They were assessed for neurotoxicity, i.e. ptosis, eye movements, pupillary size and reaction to light, power of neck flexors and limbs, respiratory rate, chest expansion, strength of speech, level of consciousness, blood pressure and local effects. The muscle power was graded from 0 to 5 using British Medical Research Council criteria and subsequently severity of neuromuscular weakness was graded as mild, moderate and severe. The alteration in consciousness was categorized as normal, drowsy, semiconscious and unconscious.

Patients with confirmed krait envenoming were given initial resuscitation if required and then administered 10 vials (100 ml) of polyvalent anti-snake venom (Bharat Serum and Vaccines Ltd.), intravenously. In 10 patients the dose was repeated within 2 h as symptoms had not improved or had worsened. In addition, patients were given three injections of neostigmine (1.5 mg each) I.V. after administration of 0.6 mg of atropine. After each administration of neostigmine, patients were assessed at 10 and 20 min for any objective improvement in ptosis, respiratory, neck muscle weakness, etc. Assisted mechanical ventilation was provided when patients had saturated oxygen below 85% or $pO_2 \geq 60$ mmHg.

The statistical analysis was undertaken using SPSS 15.0. The Ethics Committee of the Institute had approved the research project.

Results

Eighty-nine patients (M: 61; F: 28) were admitted with venomous snakebite and confirmed envenomation during the study period. Seventy-three patients had signs and symptoms of neurotoxic bites and 16 had haemotoxic signs and symptoms, i.e. bleeding or incoagulable blood. Of 73 neurotoxic bites, nine were identified as caused by *B. caeruleus*, by identifying the dead snakes brought by patients and attendants, using standard morphological keys, i.e. enlarged hexagonal dorsal scales, by the herpetologist (IDS). Sixty-three were identified to be common krait from the circumstances of the bite and morphological features described by patients if they had seen the snake and from clinical features. One was identified to be bitten by the spectacled cobra (*Naja naja*) from clinical features, i.e. local pain, swelling and subsequent development of neuroparalysis and was excluded from the final analysis. The remaining patients had incoagulable blood or systemic bleeding indicative of a viper bite with one identified Russell's viper (*Daboia russelii*). In 15, the species of viper could not be confirmed. All these patients were also excluded from the final analysis.

Of 72 patients, 48 were men and 24 were women. The mean (±SD) age of men was 30.2 ± 9.3 years (range 15—60 years) and of women was 29.4 ± 9.0 years (range 16—65 years). All the patients were admitted between late June and September. All the patients except two were from rural areas. Sixty-two patients were bitten at night (11 pm—5 am) while they were sleeping. However 11 patients were bitten while clearing bricks, cutting grass and walking. The mean interval from bite to hospital admission was 4.8 h (range 0.5—10 h).

Abdominal pain was the first symptom to manifest within a few minutes to hours in more than half of the patients. Other common clinical features were weakness of limbs and inability to stand, drooping of eyelids, difficulty in breathing and altered sensorium (Table 1). Less commonly was par aesthesia at the site of bite. In all the patients the fang marks were indistinct and local reaction was minimal to faint.

None of the 72 patients administered three injections of neostigmine at 30 min interval preceded by one injection of 0.6 mg of atropine, showed any improvement or reversal in neuromuscular paralysis following administration. Sixty-two patients received 10 vials (1 vial = 10 ml) of lyophilized polyvalent antivenom. Ten patients received another 10 vials of polyvalent antivenom within the next 2 h, as there was a deterioration or lack of improvement in the victim's condition. However despite antivenom, all victims developed respiratory paralysis and required assisted mechanical ventilation with mean duration of 39.5 h (range 8 h—20 days). Four patients developed respiratory failure before arrival at the hospital, and were intubated and supported with a resuscitation bag. Twenty-two patients required assisted ventilation (SIMV mode) for less than 24 h, 40 for between 24 and 72 h, 10 for more than 72 h, and 1 patient required assisted ventilation for 20 days. Two patients did not survive, the cause of death being hypoxic brain damage occurring before reaching the hospital.

Discussion

In Northwestern India, neuroparalytic common krait bite is an important emergency as majority of the population, approximately 70%, live in rural areas and are engaged in farming. Unlike the study by Kularatne et al. from Sri Lanka where men and women were equally affected, in our study men were bitten nearly twice more than women. This difference is probably due to the fact that men carry out the majority of agricultural activities in

Table 1 Symptoms and signs in 72 victims of *B. caeruleus* bite on admission.

Symptoms and signs	Men (48)	Women (24)	Total	%
Abdominal pain	38	14	52	72.2
Dyspnoea	10	8	18	25.0
Giddiness	2	0	2	2.9
Nausea	2	0	2	2.9
Vomiting	1	1	2	2.9
Altered sensorium	3	1	4	5.8
Ptosis	47	23	70	97.1
Weakness of neck flexors	36	14	50	70.0
Respiratory failure	7	3	10	10.4
Hypertension	6	3	9	10.2
Local reaction	0	0	0	0

Mean interval between bite and admission in hospital = 4.5 h.

this part of India. Majority of the males involved are men who migrate from the poorer eastern regions of India and work as agricultural laborers not sharing accommodation with wives or children.

Sixty-two bites occurred while the victims were sleeping and 10 occured during activities like grass cutting, clearing bricks, and walking, similar to other reported studies [1,2,5]. The mean time interval between bite and admission to hospital (4.5 h) was shorter in our study than that reported by others [5]. This is probably due to high awareness among the public in the region about the hazards of snakebite and the need for rapid hospitalization and existence of better transport facilities.

Studies of definitive krait bites have documented severe respiratory paralysis and the need for prolonged ventilatory support [3,5—8]. Electrophysiological studies have shown that envenoming bites by kraits are associated with a reduction in the compound muscle action potential and a decremental response to repetitive nerve stimulation [13]. Animal studies have shown that the venom of kraits contains three major types of neurotoxins of which α-bungarotoxin causes failure of neuromuscular transmission by binding to post-synaptic neuronal acetylcholine receptors (nAChR) at the neuromuscular junction [14]. The second neurotoxin is κ-bungarotoxin which is exclusively found in the venom of kraits. It is structurally similar to α-bungarotoxin and binds to neuronal AchR post-synaptically [15]. The third pre-synaptically active β-bungarotoxin constitutes >20% of protein content of the krait venom and causes the failure of neuromuscular transmission for long periods by depleting synaptic vesicles at nerve terminals [16—18]. It further leads to structural damage of motor nerve terminal and the destruction is complete by 12—24 h [16—20]. It has been postulated that β-bungarotoxin alone or in combination with α-bungarotoxin is predominantly responsible for severe paralysis. Recovery therefore depends on the regeneration of synaptic vesicles, which takes a significant time leading to requirement of mechanical ventilation considerably in excess of that in post-synaptic envenomings [17].

Timely administration of appropriate antivenom is the mainstay of treatment for snakebite, as there exists a good correlation between development of complications and administration of antivenom. Although antivenom was administered early in our study, it did not prevent the development of neuroparalysis. This is probably due to rapid binding of β-bungarotoxin to its binding site on nerve terminals with process being complete as early as within 5 min [21]. Despite the fact that antivenom has no effect on bound venomous antigen at the neuromuscular junction, it undoubtedly neutralizes free flowing venom. Theakston et al. [22] have clearly shown the clearance of venom antigenemia following intravenous polyvalent antivenom, leading to reduced severity. Even though all the patients developed respiratory paralysis and required assisted mechanical ventilation despite antivenom administration, the mean duration of assisted ventilation was much shorter (mean 39.5 h) than other studies. It is likely that the antivenom neutralized free flowing venom leading to its rapid clearance and thereby less severe neuroparalysis and thus shorter duration of assisted mechanical ventilation. The mortality in our study was very low (2/72) as compared to a previous study from India [6] where mortality was 77%. The reason for low mortality in our study is the better availability of ventilatory support and intensive care facilities.

In previous evaluations adequacy of response to anticholinesterase in neurotoxic envenoming bites have been raised. Beneficial effects have been demonstrated in individual patients, but the results from series have been inconsistent [5,7—12]. This is probably because of inclusion of krait bites in these series [12]. The krait β-bungarotoxin is completely resistant to them [23]. In our study, all the patients were given neostigmine. Three doses were administered in this study, given in accordance with existing practice at the hospital. The Indian National Snakebite Protocol recommends a single dose of intramuscular neostigmine, with atropine, in line with the diagnostic test for myasthenia gravis [24]. Although this study employed a higher dose regimen it did not improve the neuroparalytic symptoms. Neostigmine appears to have no useful role in confirmed pre-synaptic envenoming and in patients where the identification of the biting species is confirmed, neostigmine can be withheld.

This study was carried out at a tertiary hospital equipped with mechanical ventilation equipment. Such hospitals are few in developing countries and most frequently victims report to basic medical facilities with no mechanical ventilatory support. It is essential therefore to ensure guidelines for snakebite treatment to include measures to provide better airway support in basic settings, particularly where long journeys to better-equipped hospitals occur [24,25].

Conflict of interest

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