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CASE REPORT **OPEN ACCESS**

A LIFE-THREATENING NEUROTOXICITY IN BUNGARUS CANDIDUS SNAKE BITE: A CASE REPORT

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ABSTRACT

Background: Bungarus Candidus is a snake that induces severe neurotoxic symptoms.
Case: A 31-year-old female came to the emergency department with complaints of pain in the whole body, limb weakness, shortness of breath, and epigastric pain after being bitten by a snake. Neurological examination, ptosis of both eyelids was found with normal movement of the eyeballs. Muscle strength in all extremities is 4, followed by decreased physiological reflexes. There are fang marks in the form of 2 slightly swollen and reddened black dots on the left foot. During observation, the patient had decreased consciousness and severe shortness of breath with desaturation without any signs of shock. Other clinical revealed bilateral dilated pupils, dysphonia, dysarthria, and muscle strength that was difficult to assess. The patient was intubated and subsequently admitted to the ICU. The patient regained consciousness but still had difficulty opening his eyes and weak muscle strength on the 2nd of ICU. The patient's condition improved on the 5th of ICU, extubating was performed and transferred to the non-ICU. The treatment obtained included 17 vials of SABU, analgesics, antibiotics, anticholinesterase, and anticholinergic. The patient was discharged after 11 days of hospitalization.
Discussion: The neurotoxicity of snake venom is related to mechanisms of neuromuscular transmission blockade, pre-synaptic and post-synaptic. Bungarus Candidus has a peculiar type of toxin, candoxin, that inhibits nicotinic acetylcholine receptors at the postsynaptic site.
Conclusion: Prompt recognition of symptoms and management interventions in snakebite cases are critical to patient outcomes and survival.

Keywords: Bungarus Candidus, neuromuscular, neurotoxic, toxin

Introduction

Snakebite is a life-threatening tropical disease with high morbidity and mortality rates, particularly in rural areas. The incidence of snakebites is higher during the agricultural and rainy seasons.[1] According to the World Health Organisation (WHO), the yearly incidence of snakebite is estimated at more than 5 million, with a mortality rate of 125,000 worldwide, of which 25,000 to 35,000 snakebite deaths occur in Asia.[2] In Indonesia, an estimated 135,000 cases occur annually among a population of 273 million people (2020), equating to 50 cases per 100,000 people.[3]

It was estimated that 15% of the 3000 snake species worldwide are harmful to humans. In Southeast Asia, there are three families of venomous snakes: Elapidae, Viperidae and Colubridae, Colubridae, each with different venom toxicities and clinical manifestations. The Elapidae family is responsible for the majority of snakebites.[4] Bungarus candidus, also known as the Welling snake, is a species in the Elapidae family that can cause neurotoxic symptoms.[5] Although snakebites can cause severe and even life-threatening symptoms, rare antivenom is available for this snake species in Indonesia. However, proper treatment and

administration of antivenom in appropriate doses are effective in maintaining survival. This case report describes a patient who suffered severe neurotoxic symptoms after a bite from a Bungarus candidus snake.

Case Report

A female patient aged 31 years-old was admitted to the emergency department after being bitten by a snake with chief complaints of pain in the whole body. This was followed by limb weakness, shortness of breath and epigastric pain. The snake bite had occurred 2 hours prior to admission. At the time of the bite, the patient was sleeping on the floor of her room. The snake was around 1 meter and was black and white in color (Figure 1). The patient had no past medical history of hypertension, diabetes, heart disease or tuberculosis. The patient denied any history of food or drug allergy.

The physical examination revealed the patient was conscious with a GCS score of 15 E4M6V5. The patient's vital signs were recorded as blood pressure of 140/78 mmHg, pulse of 111 beats per minute, spontaneous breathing of 24 breaths per minute, and oxygen saturation of 98% with a nasal cannula at 4 liters per minute. The examination of the lungs, heart, and abdomen did not reveal any abnormalities. The neurological examination revealed ptosis in both eyelids and normal eye movement. The motor muscle strength of all four extremities was found at grade 4, with decreased physiological reflexes. On the plantar pedis sinistra, there was a snake bite mark in the form of 2 black dots with a length of 1 cm between them, slightly swollen and red in the bite area (Figure 2).

The hematological examination of the patient revealed blood results within the normal range. Haemoglobin 12 g/dl, hematocrit 35%, erythrocytes 4.05 x 10^6 uL, leukocytes 8.06 x 10^3 uL, platelets 228 x 10^3 uL and blood sugar 131 mg/dL. The electrolyte examination revealed a sodium level of 147 mmol/L, mild hypokalaemia of 3 mmol/L, and a chloride level of 108 mmol/L. The liver function test revealed Alanine aminotransferase (ALT) levels of 31 U/L and Aspartate Aminotransferase (AST) levels of 35 U/L. The renal function test showed urea of 27mg/dL and creatinine of 0.6mg/dL. The hemostasis function test revealed Prothrombin time (PT) of 11 seconds and Activated partial thromboplastin time (APTT) of 36.6 seconds, which were within the normal levels. Periodic blood tests were conducted to monitor the patient's condition.

The patient received initial treatment in the emergency department including oxygen via nasal cannula 3 litres per minute, intravenous fluids NaCl 0.9% 500cc/6 hours, ceftriaxone 2gr, ketorolac 30mg, ranitidine 50mg, methylprednisolone 62.5mg, antitetanus 250 iu and serum anti-venom (SABU) 2 ampoules in 5% dextrose IV over 4 hours. The patient was observed in the emergency room for three hours and had decreased consciousness with GCS score of 9 E2M4V3, severe shortness of breath with respiratory rate of 32x/i followed by desaturation of 89% without signs of shock. Additional clinical features included bilateral ptosis, bilateral dilated pupils with size 5mm and decreased physiological reflexes. intubation was performed to secure airway patency and the patient was managed in the ICU.

Following 28 hours of ventilator treatment, the patient started to respond to voice commands, but was not yet able to follow instructions. The vital signs were normal, but the physical examination revealed that the pupils were mydriatic with a size of 5mm on both sides. The patient had bilateral ptosis and decreased physiological reflexes, negative pathological reflexes, and muscle strength scored 2 points. The haematological examination reported a leucocytosis of 21.220uL. However, the renal and liver examinations showed normal results. The patient received anti-snake venom serum (SABU) continuously with 3 vials of 100cc Normal saline 0.9% administered over 2 hours and repeated every 6 hours. Prostigmin 3mg and sulphas atropine 0.75mg were administered every 24 hours.

The available snake venom serum during initiating treatment was a polyvalent snake venom serum for Naja sputatrix - Cobra, Bungarus fasciatus - Striped Snake and Agkistrodon rhodostoma - Earth Snake, therefore the administration of snake venom was not effective in this case. On the second day of treatment, the patient received polyvalent snake venom serum, which is effective on the snake species Bungarus candidus. The serum was administered in two vials in NaCl 0.9% 500cc over 6 hours. Reassessment of the patient's condition shows that the patient gradually regained consciousness, and could open his eyes slightly. Although ptosis was still present, shortness of breath, and can shift all four extremities with a motor strength of 2 points.

The patient was administered the monovalent anti-snake venom serum which is specific for Bungarus candidus on the third day of treatment. A single vial of anti-venom serum was administered in NaCl 0.9% 500 cc and completed in 6 hours. A reassessment conducted on the 4th day of treatment after the administration of anti-snake venom serum showed an improvement in muscle strength of all four extremities by 3 points, shortness of breath was decreased, and the patient was able to partially open his eyes. The weaning of the ventilator was initiated. The patient was on nasal cannula oxygen after extubation on the fifth day in the

ICU. The patient was able to open his eyes, follow instructions, could move all four extremities, and the shortness of breath resolved. The patient still had dysarthria and her voice was also very quiet. The examination of vital signs was within normal limits. The leucocyte level improved from 21.220 10^3/uL to 13.680 10^3/uL. Hypokalaemia of 2.6 mmol/L was revealed in the electrolyte examination. Potassium was corrected by administering 25 mEq of KCl intravenously and KSR tablets oral medication until it reached the normal target. the patient was planned to be transferred to a non-intensive care unit after the 6th day of ICU treatment.

During treatment in the non-intensive care unit, the patient's condition was improved, with normal vital signs as well as hematological examination results. The patient was initiated on a peroral diet. The patient's dysphonia and dysarthria had shown signs of improvement. During physical examination, the patient complained of numbness and tingling in both legs. Motor strength was assessed as 4 points and physiological reflexes were normal. The patient was discharged after 11 days of treatment.

Figure 1. Snake Bungarus Candidus (welling)

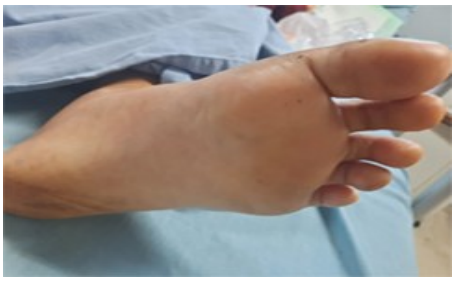

Figure 2. Snakebite marks 2 black spots

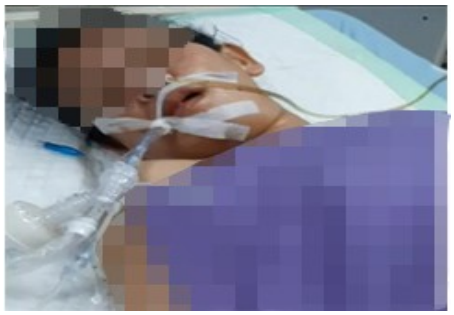

Figure 3. Intubated patient in ICU care

Discussion

Bungarus candidus snakes inhabit peninsular Malaysia, Indonesia (Sumatra, Java, and Bali), Vietnam, and Thailand.[6] It is classified as a Class I venomous snake. This means it can have a major impact, including high rates of disability and mortality, especially in Indonesia and Thailand. These nocturnal creatures are usually docile during the day, but may become aggressive when threatened and are often found in close vicinity to human habitation, especially in rural areas.[3,5] This is related to the patient's and family's statement that the patient was bitten by this species of snake at night, and it is known that the patient's living environment is close to rice fields. The main clinical manifestation of this snake is neurotoxic symptoms.[6] One study explained that bungarus snake venom's neurotoxicity is related to pre-synaptic and post-synaptic neurotransmitter blockade mechanisms.[7] Neurotoxins that bind presynaptically to motor nerve terminals lead to depletion of synaptic ACh vesicles, disruption of ACh release and degeneration of motor nerve terminals. The binding between neurotoxins and nerve terminals is irreversible.[15] Therefore, clinical improvement with presynaptic neurotoxins may take longer, depending on nerve terminal regeneration or the formation of new neuromuscular junctions.[7,8]

Acetylcholine-muscle nicotinic receptor interaction gets disrupted due to post-synaptic neurotoxins.[16] The post-synaptic neuromuscular blockade induced by neurotoxins may be reversible or irreversible.[8] Various toxins are found in Bungarus snakes, such as alpha bungarotoxin, beta bungarotoxin, kappa bungarotoxin, and candoxin. Bungarus candidus snakes have specificity towards the candoxin toxin, which belongs to the non-conventional alpha neurotoxin (3FTX) group. Candoxin toxin acts by blocking nicotine acetylcholine receptors at the post-synapse with reversible effects.[8,17] A study of 78 cases of Bungarus snake bites reported in Thailand revealed that the onset of severe neurological symptoms occurred within the first 0.5-8 hours after the bite.[5]

The patient in this case was admitted to the emergency department 2 hours after being bitten by a snake. According to the patient's history and physical examination, the patient began to present symptoms and signs of neurotoxin in the form of ptosis of both eyelids, shortness of breath, and limb weakness. Three hours later, the patient's condition deteriorated. The patient was intubated and admitted to intensive care (Figure 3). It's important to monitor the patient's clinical condition closely during this period in order to carry out subsequent medical interventions effectively. The neurotoxic manifestations of snakebite are commonly known as descending paralysis, where symptoms first affect small muscle groups and then

large muscles.[9,13] Clinical symptoms manifest rapidly.[14] Paralysis of muscles begins with the involvement of the extraocular and facial muscles, followed by the development of dysarthria and weakness of the masseter muscles that impair swallowing, progressing to the neck, bulbar muscles, respiratory muscles and limb muscles.[7,9] This explains the reasons why the patient in the case report had decreased consciousness, ptosis, respiratory distress and limb weakness.

The blood test indicated mild hypokalaemia, with a potassium level of 3.0 mmol/L that decreased to 2.6 mmol/L. Hypokalaemia in snakebites caused by neurotoxins arises from potassium shifting into cells alongside beta-adrenergic stimulation triggered by autonomic dysfunction.[10,18] In a study conducted, it was reported that hypokalaemia is actually rare and can occur in Bungarus candidus snakebites in mild degrees. This is in contrast to Bungarus caeruleus and Bungarus sindanus.[5] The antivenom for snake venom is ideally administered within 4 hours after the snake bite and only if there are both local and systemic symptoms.[4] Other sources state that antivenom should only be given if there are systemic symptoms.[3] Administering the anti-venom may also be considered if there are hemostasis abnormalities, neurotoxic signs, cardiac abnormalities, acute renal failure, hemoglobinuria, or swelling of the area around the snake bite.[19,20]

Table 1. Classification of snakebite severity[11]

Elipdae family		
Grading	**Severity**	**Sign and symptoms**
0	None	History of snakebite, local edema with strokes, no neurological disorder
1	Moderate	Grade 0 with a neurological sign or with euphoria, vomiting, nausea, paraesthesia, ptosis, paralysis, or dyspnoea.
2	Severe	Grade 1 symptoms with respiratory muscle paralysis in the first 36 hours

In this case, patient had severe systemic symptoms, including clinical respiratory failure classified as grade IV snakebite (Table 1). The patient received 12 vials of bio save polyvalent snake anti-venom serum (for Naja sputatrix - Cobra, Bungarus fasciatus - Striped Snake, and Agkistrodon rhodostoma - Earth Snake), 2 vials of Bungarus candidus-specific polyvalent snake anti-venom, and 1 vial of Bungarus candidus-specific monovalent snake anti-venom serum.

Conclusion

There are only a limited number of documented cases of snakebite-associated neurotoxicity in Indonesia. Documenting additional cases could not only improve the management of neurotoxic snakebites, but also assist in the identification of various neurological manifestations.

Declaration of Interests

We have no relevant financial interest to disclose.

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