Asian Biomedicine Vol. 6 No. 6 December 2012; 795-805 DOI: 10.5372/1905-7415.0606.125

Review article

Diagnosis and management of venomous snakebites in Southeast Asia

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Background: Globally, snake envenoming is an important medical problem. Various species from different parts of the world require a variety of diagnostic and therapeutic strategies.
Objective: Review clinical manifestations, diagnosis, and management of venomous snakebites in Southeast Asia.
Method: Relevant information was extracted from publications in the PUBMED database (up to June 2012) and the World Health Organization (WHO) website. Expert opinions of the authors were added when clinical trial evidence was lacking.
Results: The clinical findings including local tissue damage, muscular weakness, coagulopathy, and renal injury were summarized. These data can be used to deduce the responsible snake species. The guide for the first aid, initial evaluation, follow-up observation, and antivenin administration was also suggested.
Conclusion: It is critical to transport snakebite victims to hospitals as soon as possible for basic and advance life supports. Appropriate usage of antivenin is life-saving. However, a mode to prevent debilitating tissue necrosis remains to be defined.

Keywords: Antivenin, diagnosis of snakebite, management of snakebite, Southeast Asia, venomous snakebite

Venomous snakebite is still a major, but neglected, public health problem worldwide [1]. It has been estimated that it causes over 50, 000 deaths per year [2]. The highest number of snakebite victims is in South and Southeast Asia [2], a densely populated and agricultural region. Prompt and proper management is critical to decrease mortality and disability from envenomation.

Snakes from different geographical locations display diverse behavior and venom compositions resulting in dissimilar signs and symptoms. Therefore, they required evidence based diagnosis, evaluation, and treatment schemes, as well as specific antivenins. This article will focus only on the bites by common species in Southeast Asia. A review on medically important species in this area was recently published [3].

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Clinical manifestations

Manifestations of venomous snakebites are helpful in suggesting the responsible species, which are commonly unidentified on presentation to the hospital. The signs of snakebites can be divided into those caused by local and systemic effects of the venoms.

1. Local symptoms analysis starts with appearance of fang marks, typically two needle-stick dots inflicted by the fangs (**Figure 1**). This is a specific sign of venomous snakebite. Subsequently, patients may develop pain, swelling, and warmness of the bitten limbs. In more severe cases, skin blistering and dermonecrosis occur from local tissue damage (**Figure 2**). Furthermore, snakes that affect the hemostatic system can cause ecchymoses and hemorrhagic blebs. The severity of local effects is different among species (**Table 1**). This information is beneficial in diagnosis and prognostication of the types of snake.

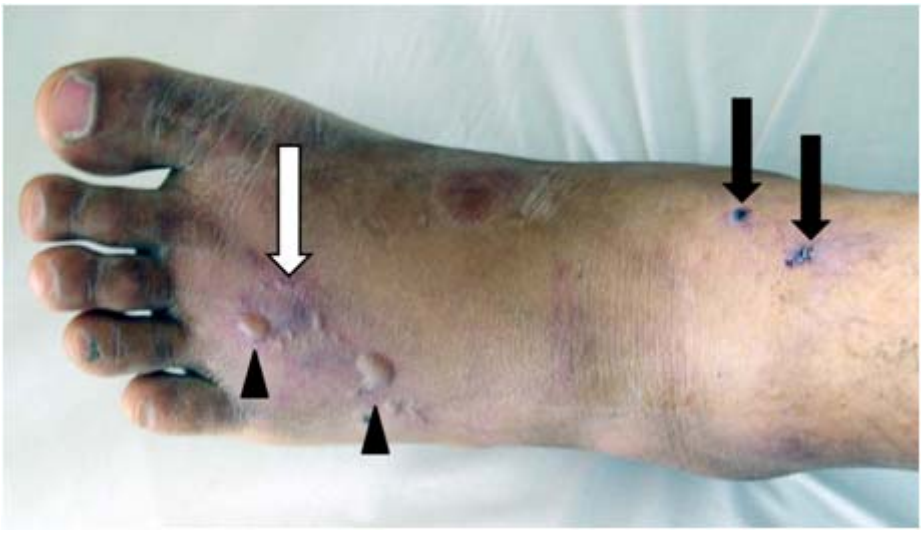

Figure 1. Local effects of Green pit viper (*Cryptelytrops albolabris*) bites showing fang marks (Black arrows), ecchymosis (White arrow) and blisters (Arrow head).

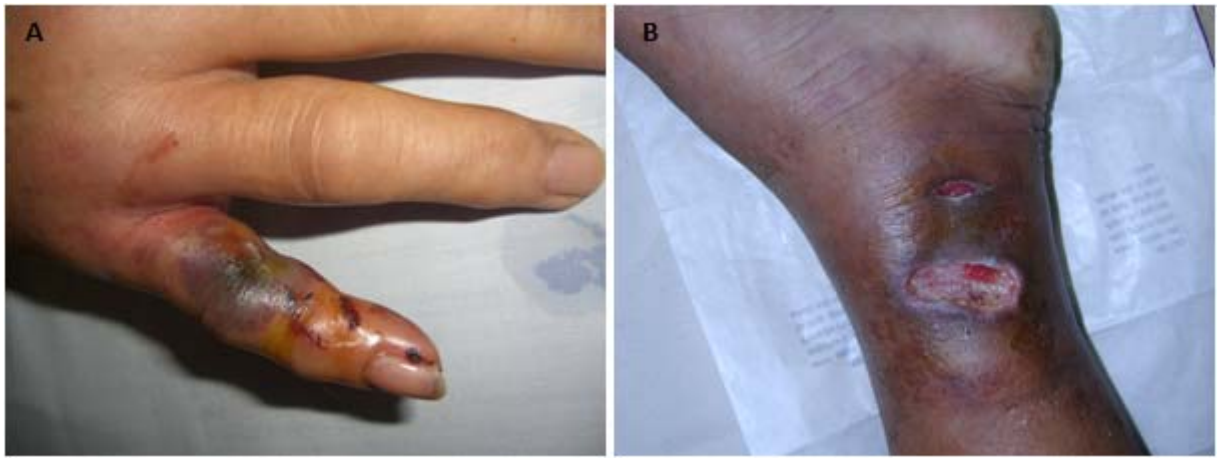

Figure 2. Local tissue necrosis caused by Cobra bites. **A:** Early necrosis showing purplish discoloration. **B:** Late dermatonecrosis that may require skin grafting.

Table 1. The local effects from venomous snakebites in Southeast Asia

Local effects	Suggested species
Fang marks	Venomous snakes
Minimal local effects	Kraits, Colubrids, dry bites
Severe local effects	Cobra, King cobra, Malayan pit viper
Bleeding from fang marks, hemorrhagic bleb, ecchymoses	Vipers or pit vipers

2. Systemic effects are the results of absorption of venoms into circulation. Snake venom main targets are neuromuscular junctions causing paralysis, and the hemostatic system causing bleeding tendency. In addition, envenomation may give rise to renal failure, rhabdomyolysis, and/or hypotension.

Many snake venoms involve multiple systems. However, the species in Southeast Asia are usually toxic mainly to either neuromuscular or hematologic systems. This is very helpful in snake identification in clinical practice and treatment planning.

2.1 Neurotoxicity is usually caused by Elapids namely cobra, king cobra, and kraits. The toxins attack neuromuscular junctions. Initially, small muscles are involved resulting in ptosis (**Figure 3**) followed by dysphagia, dysarthria, generalized weakness, and respiratory muscle paralysis leading to death. Some elapid victims suffer from complete paralysis with fixedly dilated pupils, but are still alive.

Cobra venoms contain reversible post-synaptic neurotoxins. Neuromuscular weakness can spontaneously recover within 2 to 3 days [4]. In contrast, the effects from krait pre-synaptic toxins are irreversible. Respiratory failure after krait bites may persist for weeks [5, 6]. Furthermore, there was a report of Malayan krait envenoming that resulted in parasympathetic nervous system dysfunction, e.g. hypertension, tachycardia, mydriasis, and constipation that may persist for years [5-7]. Sea snake bites cause muscle damage. Rhabdomyolysis results in generalized muscular pain, dark urine from myoglobinuria and renal failure.

2.2 Hematotoxicity is typically caused by vipers and pit vipers. Patients present with bleeding, commonly of gingival, gastrointestinal, and urinary origin. In addition, Russell's viper bites may also cause acute renal failure and hemolysis. There are geographical variations of the Russell's viper venom among different countries in this region. For examples, ptosis is found only in India and Sri Lanka, while pituitary gland infarction and vascular leakage are reported in Myanmar [8]. These symptoms have never been found in Russell's viper bites in Thailand.

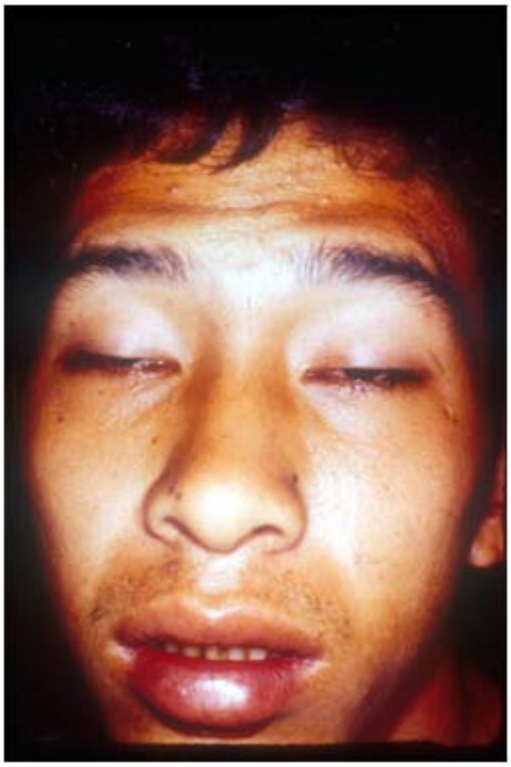

Figure 3. Ptosis caused by Cobra bite

Laboratory features

1. Viper bites activate coagulation factors resulting in consumptive coagulopathy [9]. Green pit vipers and Malaya pit viper venoms change fibrinogen to fibrin stimulating fibrinolysis causing the defibrination syndrome [10, 11], while Russell's viper venoms activate clotting factor V and X triggering disseminated intravascular coagulation (DIC) [12]. Platelets are also activated and subsequently cleared from the circulation. These mechanisms lead to prolonged coagulation time and thrombocytopenia. Furthermore, microangiopathic hemolytic anemia (MAHA) may be found in Russell's viper bite victims resulting in anemia and schistocytes on peripheral blood smears (**Figure 4**). Apart from a complete blood count (CBC), the 20-minute whole blood clotting test (20WBCT) was recommended by the World Health Organization (WHO) for patient evaluation [13]. 20WBCT is widely available even in a remote area and found to well correlate with fibrinogen levels [14]. Not clotted blood in a glass tube after 20-minutes suggests severe hypofibrinogenemia requiring antivenom therapy (**Figure 5**). Alternatively, prothrombin time (PT) may be used. It also reflects fibrinogen levels and has better standardization compared with the whole blood clotting time [15].

2. Renal failure may be found in Russell's viper and sea snake bites (with rhabdomyolysis). Therefore, renal function should also be evaluated. In addition, muscle enzymes and electrolytes should be measured, particularly in sea snake victims. Patients with sea snake bites often develop severe hyperkalemia, which can be fatal if not identified.

Diagnosis

Diagnosis requires determination whether the snake is venomous and the identification of snake species.

The diagnosis of venomous snakebite can be made from the snake carcasses brought with the patients or patient clear description or identification of the snake. However, the former is uncommon and the

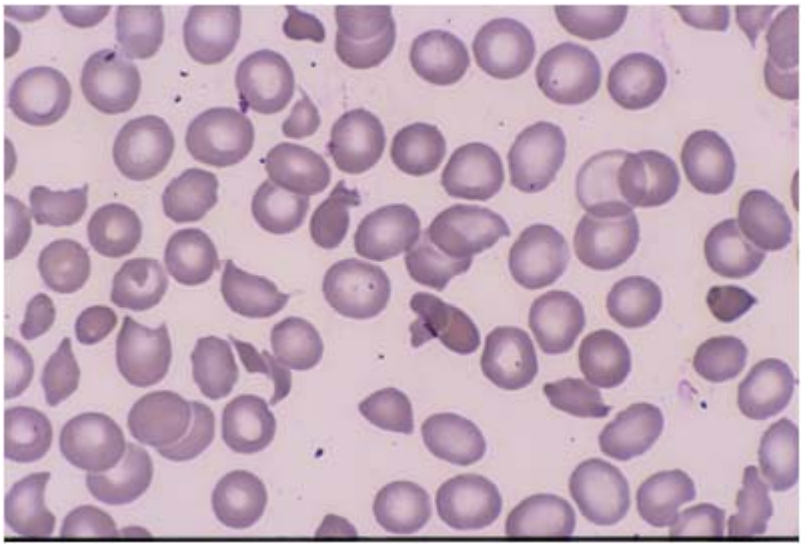

Figure 4. Microangiopathic hemolytic anemia (MAHA) caused by Russell's viper bites

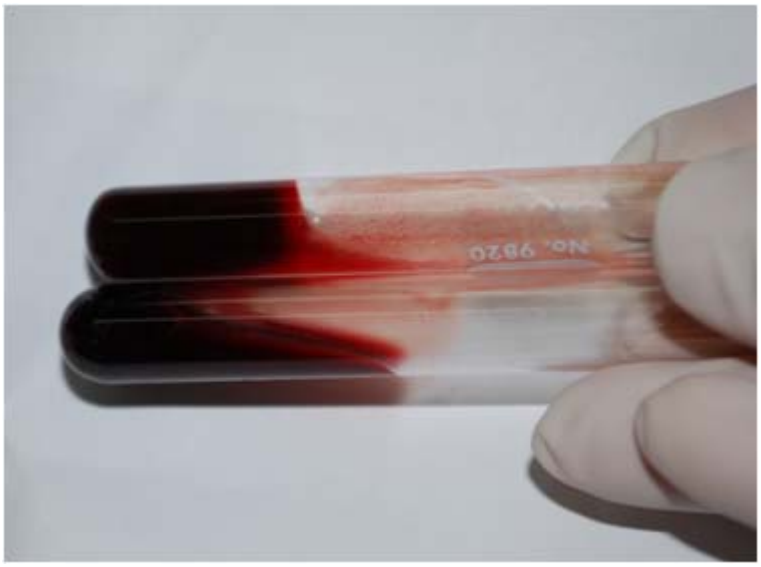

Figure 5. Twenty minutes whole blood clotting test (20WBCT): Glass tubes containing non-anticoagulated blood are tilted after standing for 20 minutes. The upper tube is normally clotted, while the lower tube is still un-clotted indicating coagulopathy.

latter is often unreliable. The fang marks strongly suggest venomous snakebite. Finally, the systemic signs and symptoms, weakness versus bleeding, not only indicate venomous snakes, but also suggest the responsible species.

The places of bites may be helpful in estimating the snake species. For examples, green pit vipers are responsible for over 90% of venomous snakebites in Bangkok. A venomous snake on a tree suggests a green pit viper, while a snakebite in a house during the night implies a Malayan krait. Furthermore, different local signs may hint different types of snakes (**Table 1**).

Enzyme-linked immunosorbent assays (ELISA) of blood samples have been developed to determine the species of the biting snakes [11]. However, they are not generally available and the turnaround time is too long for clinical decision making. They are used mainly for research or retrospective identifications in problematic cases.

Polyspecific antivenins that can neutralize multiple species of venoms are helpful in clinical practice. They can be administered without information on the specific species responsible for the bite (see details below).

Management

1. Pre-hospital management (First aid)

The first objective at this stage is to save the victim's life. The complications that might cause rapid death are respiratory muscle paralysis and/or severe hypotension. The treatments of these conditions require personnel who are trained for airway management, assisted ventilation, and intravenous fluid and medication administration.

The second priority is to transfer the patient to a health care facility because there is still a risk of imminent death from these complications. Snakebite victims may be completely paralyzed, breathe very slowly and/or display impalpable pulses due to the effects of venoms. It is essential not to assume that the patient has already expired. All patients should be helped and transferred to the hospital as fast as possible. The ignition key for a functioning automobile or boat may be the most important first aid equipment.

The third priority is to retard the venom absorption from the wound. Tight tourniquet cannot prevent systemic absorption of the venom and may cause ischemic necrosis of the affected limb [16-18]. They are no longer recommended. The method that is proven to delay systemic envenomation in an animal model is termed pressure immobilization [19]. This procedure requires an elastic bandage or a long piece of cloth to wrap the bitten limb from the lower to upper part at the pressure of 55 mmHg combined with a long rigid object to splint that limb (**Figure 6**). The technique is difficult to perform properly even by health care workers [20]. If an attempt to carry out the pressure immobilization delays the transportation, it should be omitted in order to bring the patient to a hospital as soon as possible.

To bring the snake carcass to doctors may be helpful for species identification as long as this does not pose a risk of another bite or retard the time to a hospital. Physicians can manage the patients without knowing the snake species. During the transportation, the victim should receive reassurance and control of distressing symptoms.

Another important point is to 'Do no harm'. Many methods may cause more damages to the tissue without any benefit. In addition to arterial tourniquet, a wound incision, suction, application of fire, electricity, chemicals, and herbs should be avoided.

Figure 6. Pressure immobilization as a first-aid for venomous snakebite

2. Hospital management

2.1 General managements

2.1.1 Basic and advanced life support

Patients should not be assumed to be dead based on their unresponsiveness. Airway, breathing, and circulation (ABC) should be checked and resuscitated. Intravenous fluid or blood products are for hypovolemic shock and adrenaline for anaphylaxis from snake venom.

2.1.2 Reassurance of the patients and relatives

2.1.3 Untying the tourniquet and cleaning the wound

Prolonged tourniquet may aggravate limb edema and ischemia and should be removed on hospital arrival. Notably, there was a report of rapid respiratory failure after a tourniquet release in a cobra (*Naja phillippinensis*) victim [21]. Therefore, assisted ventilation should be promptly available in cases of neurotoxic snakebites.

2.1.4 Affected limb elevation and analgesics

Elevation may aid resolution of limb swelling. Analgesics with central nervous system depressing activities should be avoided in cobra and krait bites due to a risk of respiratory failure. Aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) should not be given in viper bites because of a bleeding risk.

2.1.5 Tetanus toxoid

There was a reported case of tetanus after green pit viper bite [22]. The toxoid is needed to be injected intramuscularly and, therefore, delayed until clotting time is normal in viper bites.

2.2.7 Antibiotic prophylaxis is not recommended, as the secondary infection rate is very low [23].

2.2.8 Corticosteroids are not helpful. A randomized controlled trial in children who were bitten by green pit vipers did not show a benefit of oral prednisolone compared with placebo [24].

2.2 Initial evaluation and observation

A patient should be examined for local and systemic symptoms and signs of snakebite (see the above section). The expiratory peak flow measurement is useful to evaluate respiratory muscle weakness in neurotoxic snakebites. A conventional venous clotting time [25], 20 minutes whole blood clotting test [14] or prothrombin time [15] may be used for diagnosis and severity assessment of hematotoxic snakebites. Renal functions should be tested in suspected Russell's viper bites and sea snake bites, which require muscle enzyme assays and following serum potassium levels.

Snakebite victims frequently show no systemic signs and laboratory abnormalities upon arrival at hospitals. However, fatal complications may subsequently occur and they require clinical observation for a period of time. In Thailand, antivenin will be given only for signs of systemic envenomation except in Malayan krait bites.

The patients should be observed for local complications. Cobra or Malayan pit viper bites often cause painful tissue necrosis. Pit viper bites may result in marked limb swelling compromising the blood supply. A rapidly progressive swelling of the limb may suggest systemic coagulopathy after viper bites.

For neurotoxic snakebites, all patients should be admitted to the hospital to closely observe any signs of muscular weakness, such as ptosis. This should be continued for at least 12 hours after bites [4]. Ventilatory failure is a serious complication that may be monitored using frequent peak expiratory flow rate measurements. An endotracheal tube and a ventilator should be readily available when indicated.

For hematotoxic snakebites, the patients should be observed for 3 days after bites because the longer half-lives of the venoms [23]. Green pit viper bites may be monitored daily as outpatients. Systemic bleeding, especially gum bleeding and ecchymosis, should be recorded.

For Russell's viper or sea snakes that may cause kidney injuries, fluid and electrolyte balances are to be monitored. Hydration and force diuresis may be helpful in prevention of renal failure. Urinary alkalinization is needed in cases of rhabdomyolysis or intravascular hemolysis.

2.3 Antivenin therapy

Antivenin is the key treatment of snake envenomation. Current antivenins are polyclonal antibodies (IgG) purified from immunized sheep or horses (in Thailand it is from horses). Monoclonal antibodies are unlikely to be effective because snake venom is a mixture of several toxins. The production of antivenin requires a snake farm as a source of venom immunogens and a large animal farm to generate antibodies. Therefore, the cost is high and usually requires a non-profit organization, such as Queen Saovabha Memorial Institute (QSMI) of the Thai Red Cross Society.

There are two types of antivenin. Monospecific antivenins are effective against one species or genus of snakes. Therefore, species is to be identified in clinics using snake carcasses and knowledge of epidemiology and/or clinical manifestations (see the above section). Currently, QSMI produces antivenin specific to king cobra, cobra, Malayan krait, banded krait, Russell's viper, Malayan pit viper, and green pit vipers. Polyspecific antivenin is able to neutralize more than one species of venoms. It is produced via immunization using multiple venoms in one animal. Therefore, a generated antibody may neutralize toxins from several species, a phenomenon termed 'paraspecificity' [27]. Consequently, polyvalent antivenin contains less protein load compared with a mixture of species-specific monovalent antivenins. As Thai snake venoms are either neuro- or hematotoxins, QSMI manufactures two polyvalent antivenins for neurotoxin [28] and hematotoxin snakes respectively. Polyspecific antivenin is more difficult to produce and, hence, more costly. Therefore, it should be used only when the species of snakes are unknown.

Different manufacturers may utilize different methods of IgG purification for the plasma of immunized animals. Caprylic acid purification yields antivenin with better physico-chemical properties compared with the use of precipitation with ammonium sulfate. Furthermore, two randomized controlled trials showed that caprylic acid-purified anitivenom resulted in lower adverse reaction rates [29, 30].

In addition, there are two distinct modifications of IgG molecules to remove the Fc portion that is implicated in acute adverse reaction to antivenin. Trypsin digestion of IgG yielding $F(ab)'_2$ has been shown to reduce the reaction rate in a randomized controlled clinical trial [30]. On the other hand, the papain-digested Fab is found to have a shorter half-life. Consequently, venom effects may recur after a Fab antivenin administration and scheduled multiple dosing is required [31]. Recurrence of symptoms is uncommon after an $F(ab)'_2$ antivenin [23].

Due to ethical limitations, there is no randomized controlled trial to prove the efficacy of antivenins. Reports are based on comparison with historical controls when antivenin is not available. For cobra bites, the average time requiring assisted ventilation in patients receiving the antivenin was 10 hours comparing with 40 hours for the historical control [32]. Notably, the effects of antivenin are not immediate. Patients may still require assisted ventilation after antivenin administration. The krait venoms irreversibly destroy the pre-synaptic neurons resulting in markedly delayed recovery even after antivenin administration, which neutralizes circulating venom. Therefore, antivenin should be given as soon as possible, preferably before the onset of symptoms in krait bites.

Without antivenin, there was a report of viper bitten patients displaying incoagulable blood for two weeks [33]. However, antivenin can promptly reverse snakebite-induced coagulopathy within 6 to 12 hours [25, 34, 35]. The data on renal failure are unclear. In a small non-randomized trial, antivenin within 6 hours after bites may alleviate the degrees of renal injury in Russell's viper bitten patients [36].

For local effects of venoms, a randomized double blind placebo-controlled trial in Thailand found that antivenin could significantly hasten the resolution of limb edema from green pit viper bites on day 1 and 2 after antivenin administration [37]. Although the result may not be clinically significant, this is a proof-of-principle that antivenin may be effective for severe limb edema with impending compartment syndrome. On the other hand, a non-randomized clinical study showed that dermatonecrosis still occurred after antivenin infusions for coagulopathy [38]. This is consistent with an animal model showing that antivenins are not active against local tissue damages due to the rapid actions of venom proteolytic enzymes [39].

The major limitation of antivenin usage is the early adverse reactions that occur within hours after infusion. The symptoms include urticaria, rashes, fever, chills, bronchospasm, and hypotension that may be fatal. The incidence ranges from 3.5% to over 80% depending on the purity and the modifications of antivenins [30, 40, 41]. Most of the patients with reactions are negative for immediate-type hypersensitivity skin tests, suggesting that it is not IgE-mediated. The pathogenesis is believed to be via complement activation by the Fc portion of IgG molecule [42]. However, complement activation has never been demonstrated in patients. Furthermore, the addition of beta propriolactone to prevent complement activation cannot reduce the rate of early adverse reactions to antivenin [43].

QSMI produces the caprylic acid-purified $F(ab')_2$ antivenins. The incidence of early adverse reactions was only 3.5% in a retrospective analysis [28]. Cobra antivenin causes more reactions than those of viper products with incidence of 12.5% and 2.3%, respectively. This may be explained by the higher

protein content per dose of cobra antivenin. The late reactions or serum sickness is also reported days to weeks after snake antivenin. However, the incidence remains to be determined.

The decision to give antivenin has to be balance between the efficacy and the side effects of antivenins. Early adverse reactions from antivenin are potentially fatal. In addition, approximately 50% of snakebites are 'dry bites' meaning that there is no venom injection. Furthermore, antivenin is not helpful for local tissue damage. In Thailand, antivenin is usually administered only when there are signs, symptoms, or laboratory values suggesting systemic envenomation. The exception is a Krait bite that requires prompt antivenin in all cases due to their irreversible or slow-recovering symptoms once these occur.

Antivenin should be given for cobra bites when there are any signs of muscular weakness. The indications for antivenin in viper bites are systemic bleeding or unclotted WBCT or prolonged prothrombin time or thrombocytopenia (Platelet below 50×10^9/L) or impending compartment syndrome. The reasons to give or not to give antivenin must be discussed thoroughly with the patients. Purified antivenin with uncommon adverse reactions may be considered in pre-symptomatic patients bitten by cobra or Russell's viper according to the physician judgment and patient preferences to prevent respiratory and renal failure, respectively.

An immediate hypersensitivity skin test is currently not recommended for antivenin as it is not predictive of any reactions [40, 42]. In addition, every patient requires close observation irrespective of the test results. A pre-medication may be useful to prevent early adverse reactions. The only medication that showed convincing data in randomized controlled trials is 0.25 ml of 1: 1000 adrenaline subcutaneously [44, 45]. Due to its potential side effects, adrenaline prophylaxis is indicated only for crude antivenins with high rates of reactions. The data on anti-histamine and corticosteroid are conflicting [45-47].

The dose of antivenin is determined by the amount that can neutralize one simulated bite. For viper bites, three vials of QSMI antivenin can restore normal blood coagulation in 50% of patients [24]. Whole blood clotting time or PT should be monitored every six hours and antivenin may be repeated for persistently not clotted blood. Sometimes, a partially clotted test after antivenin is mistaken as incoagulable blood resulting in excessive antivenin dose. In these cases, the PT will return to normal. Platelet count should also normalize after antivenin. A single dose of 10 vials of QSMI antivenin is required for cobra and krait bites. Repeated doses have no proven benefit.

Antivenin may be given through intravenous infusion with 100 to 200 ml of saline over 30 to 60 minutes or by slow intravenous injection [42]. A recent randomized controlled trial showed that there was no difference in the rates antivenin reactions using slow (2 hours) *vs.* rapid (20 minutes) administration [48]. Nevertheless, all patients should be monitored for early adverse reactions for two hours after completion of antivenin administration.

2.4 Prevention and treatments of complications

2.4.1 Local tissue necrosis

This is common after bites by cobra, king cobra and Malayan pit vipers. For green pit vipers, a bite at fingers or toes is associates with 4.5-fold increase in the risk of dermatonecrosis [25]. Currently, there is no effective means of prevention. Physicians should examine the bite wound daily for signs of tissue damages. Blisters that associate with necrosis [25] should be un-roofed and covered with sterile gauze to prevent secondary infections. Wound dressing and debridement are helpful. Amputation is usually unnecessary. Skin grafting may be used for a large area of necrosis.

2.4.2 Compartment syndrome

It is caused by muscle damages from the venom resulting in muscular edema and circulatory impairment by markedly increasing sub-facial pressure impairing blood supply to the limb. The symptoms and signs are severe pain, especially on light pressure or passive stretching, numbness, impalpable pulses and slow capillary refill time. The definite diagnosis requires intra-compartmental pressure measurement, but the instrument for this test is generally unavailable. Treatment includes limb elevation and antivenin that can reduce the edema and correct coagulopathy in case surgery is required [37, 49]. Fasciotomy is reserved only for medical treatment failure.

2.4.3 Secondary infections

In general, there is no proven efficacy of antibiotic prophylaxis [50]. Antimicrobials should be administered when there is a sign of infections. However, secondary infection is an important factor aggravating necrosis in cobra and king cobra bites and antibiotics should be given early at onset of signs

of infection [51]. Notably, blisters and necrosis increase risks of infections and antibiotics may be considered [25]. Bacteria in snake mouths come from stool of preys, which become incontinent while being swallowed. Normal flora in the mouths of green pit viper and Malayan pit viper are a mixture of gram positive, gram negative and anaerobic bacteria [22, 52]. Therefore, a broad-spectrum antimicrobial agent, such as Amoxicillin-Clavulanic acid, is preferred.

2.4.3 Renal failure

This complication is common in Russell's viper and sea snake (rhabdomyolysis) envenomation. Hydration and forced diuresis are encouraged, as one of the causative pathogenesis is impaired renal blood flow. Urinary alkalinization is indicated in hemoglobinuria and myoglobinuria. Fluid and electrolyte balance should be maintained. Low-dose dopamine and furosemide may be helpful for early oliguria. However, dialysis is required for uremia, volume overload, or severe electrolyte imbalance.

Conclusion

Venomous snakebite is still common in Southeast Asia. Various local and systemic manifestations of the victims are helpful to diagnose the types of snakes in this area. Successful treatments depend on a rapid transfer to a health care facility, basic life support, and optimal uses of systemic antivenins. Local tissue damage is currently a clinical problem where further studies are wanting.

Acknowledgment

The authors are grateful to Professor Henry Wilde for the English editing. The authors declare no conflict of interest.

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