Crotalid Envenomation In The Dog

Joshua B. Pierce

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Advisor:

Dr. Marc Seitz, DVM, DABVP (Canine and Feline Practice)

INTRODUCTION

Venomous snakes exist in 47 of 50 states, excluding Maine, Alaska, and Hawaii. (1) Given that 150,000-300,000 domestic animals are bitten by venomous snakes yearly, (2) veterinarians should be apprised of the types of venomous snakes in their respective areas of practice and should possess the ability to mitigate the effects of venomous snake bites when presented.

Ninety percent of the reported snake bites are credited to the pit viper family, Crotalidae. (2) The Crotalidae family includes rattlesnakes, pygmy rattlesnakes, massasauga, copperheads, and water moccasins (2). Mississippi is home to many species of Crotalidae; including the Eastern Diamondback rattlesnake, Timber rattlesnake, Pigmy rattlesnake, Southern Copperhead, and the Eastern/Western Cottonmouth. Of these, the Eastern Diamondback rattlesnake is the most often associated with mortality. (3) The Timber rattlesnake carries the distinction of being the only of these snakes to be neurotoxic, producing a type of muscle fasciculation known as myokymia. (3)

Crotalid family snakes may be identified by their triangle shaped head, elliptical pupil, heat sensing pit between eye and pupil, retractable fangs, and single row of subcaudal plates. This description contrasts with nonvenomous snakes' rounded head, round pupil, no heat sensing organ, no fangs, and double row of subcaudal plates. (4)

PATHOPHYSIOLOGY

Snake venom is a highly modified, species-dependent saliva, with variable composition. (5) The purpose of snake venom is to immobilize the snake's prey while concurrently partially digesting the prey. (6) The toxic elements in snake venom are enzymatic and nonenzymatic proteins that can be neurotoxic, cardiotoxic, hemorrhagic, procoagulant thrombins, and

cytolysins; the latter being the proteins responsible for most of the clinical signs. (5) Enzymes with detrimental effects in snake venom include Phospholipase A2, Thromboxane A2, hyaluronidase, and collagenase. Phospholipase A2 is implicated in cytotoxicity and red cell abnormalities such as echinocytosis, spherocytosis, and ghost cells. Phospholipase A2 formation leads to formation of Thromboxane A2, a contributor to platelet aggregation leading to thrombocytopenia from consumption. (6) Other enzymes such as collagenase break down tissues allowing venom dissemination, and proteases cause tissue necrosis and coagulopathies. Many organ systems are affected directly and indirectly by toxins including the cardiovascular system, respiratory system, nervous system, and musculoskeletal system. (5) Venom causes local tissue injury, increased vascular permeability, hypotension, coagulopathies, hematologic disorders, altered cardiac dynamics, nervous system dysfunction, respiratory depression, and myonecrosis. (6) (6) Hypotension, one of the more common clinical signs, results from hypovolemia secondary to pooling of blood in the “shock organ”, translocation of fluid into the interstitium, or blood loss. (7)

Of the crotalids, rattlesnakes have the most potent venom, followed by water moccasins, and then copperheads. (1) The amount of venom injected can be controlled by the snake. A defensive strike may be non-envenomating while an offensive bite will deliver a controlled amount. An agonal bite delivers the entire volume. (1) More venom is available for injection if a snake has not recently eaten. (6) In humans, 20% of pit viper bites are “dry bites”, with no venom injected, and another 25% are considered mild envenomation. (7) Other factors include the size of the venom sacs, the ability to compress the sacs voluntarily, and the age of the snake. (6) Venomous snakes become more aggressive and inject more venom per bite during warmer months. As an example, 90% of venomous bites occur April to October. (1)

HISTORY AND CLINICAL PRESENTATION

Upon presentation of a patient with a snakebite or possible snakebite, emergency stabilization may be necessary and a thorough history should be taken after this has occurred. The history should include the following: time of the bite, general description of the snake, first aid measures used, coexisting medical conditions, drug and food allergies, and history of snakebite and subsequent therapies, especially anti-venom and blood products. (4) The history is often suggestive of snakebite, but the diagnosis is largely presumptive based on physical exam findings and clinical signs. (8) Definitive diagnosis requires positive identification of the snake and clinical signs of envenomation as (4) there is no diagnostic test that can definitively confirm diagnosis of pit viper envenomation. (1) Pet owners may try to bring the snake in for identification. Snake parts should not be handled as the bite reflex may remain intact in recently killed snakes, allowing them the capability of inflicting a bite post mortem. (4)

Clinical signs of crotalid envenomation include pain at the site of the bite, progressive edema, ecchymosis, petechiation, weakness, dizziness, nausea, fasciculations, regional lymphadenopathy, alterations in respiratory rate, decreased hemoglobin concentration, increased salivation, cyanosis, bleeding, obtundation, and convulsions. (7) Human snake bite patients report perioral paresthesia, tingling of the fingertips and toes, and a “rubbery,” “minty,” or “metallic” taste. (4). Rapid onset of clinical signs is a good indicator of bite severity. (8) The severity of venomous snake bite is related to the volume of venom injected, the toxicity of the venom, and location of bite. (1) Severity of envenomation remains important to evaluate as an increased amount of venom requires an increased amount of antivenom. Severity of local signs do not necessarily directly associate with severity of systemic envenomation.(8)

The physical exam should be pointed toward the cardiovascular, pulmonary, and neurological systems. (4) A patient presenting with clinical signs consistent with snake bite should be examined for fang marks, puncture wounds, and scratches, (4) though, fang marks are not tantamount to envenomation. (7)

Triage tools that assist with the initial evaluation include an electrocardiogram, a blood pressure monitor, and an SpO_2 monitor. An electrocardiogram evaluates patients for arrhythmias, of which ventricular tachyarrhythmias are most common. Blood pressure monitoring helps diagnose hypovolemic shock by screening for hypotension. Finally, an SpO_2 monitor can help screen for hypoxemia.

DIFFERENTIAL DIAGNOSES

Differential diagnoses for snake bite include other animal bites, penetrating wounds, draining abscesses, trauma, and angioedema. (7)

CLINICOPATHOLOGIC ABNORMALITIES.

Coagulopathies are a very common sequela to snake bite. 60% of snake bite envenomations result in a coagulopathy. (7) 81% of envenomation result in a hematologic abnormality. (6) The most common cause of coagulopathy is hypofibrinogenemia. (7) Hematologic abnormalities reported, in addition to hypofibrinogenemia, include red cell abnormalities such as echinocytosis in 89% (6), thrombocytopenia in 30% (1), and prolonged PT in 33%, and prolonged PTT 25%. (6) Echinocytosis after envenomation, resulting from ATP depletion and phospholipase activation, has been reported to occur within 24 hours and resolved by 48 hours. (6) Damage of vascular walls by toxic venom proteins causing vasculitis has been demonstrated by electron microscopy. (4) Vasculitis is a proposed mechanism of thrombocytopenia along with sequestration and destruction of platelets. (5) Disseminated

Intravascular Coagulopathy (DIC) has been historically described in crotalid envenomation, but has recently been replaced with the term Venom Induced Coagulopathy (VIC). (5) The major difference between DIC and VIC is a normal D-Dimer concentration in VIC opposed to increased D-Dimer concentration in DIC. (6) Anemia may be seen due to hemorrhage; hemolysis is rarely seen without DIC, which is rare in snakebite victims. (3)

Many abnormalities are common on serum biochemistry after envenomation. Rhabdomyolysis may cause a rise in Creatine Kinase and AST. Hyperkalemia is seen due to muscle damage (5) and due to epinephrine release, which causes insulin release, driving potassium into the cell. (1) Hypoalbuminemia is reported due to increased loss from vessels due to vasculitis and capillary damage (5). Hyperglobulinemia is attributed to increase in acute phase proteins. (5). Urinalysis may reveal hematuria, hemoglobinuria, myoglobinuria, proteinuria, and glucosuria. Pigmenturia is associated with more severe envenomation. (3)

Recommended testing at presentation should include complete blood count with differential and platelet counts, serum biochemistry with electrolytes, blood cytology to evaluate red blood cell morphology, urinalysis, and a coagulation profile with PT, and PTT, and ideally fibrinogen, fibrin degradation products, and D-dimers. (6) Serial testing is recommended to evaluate the response to treatment over time. (6) If the bite is found, baseline circumferential measurements should be taken around the bite mark to monitor the progression of swelling (4). Severity score should be assessed at 0,6,12, and 24 hours after presentation. (1)

TREATMENT

First aid measures of the bite wound that were previously advocated but now contraindicated include ice, hot pack, incision and suction, tourniquets, and electroshock. (1)

Recommendations for field first aid include keeping the snake bite victim calm, keeping the bite site below the level of the heart when possible, and seeking veterinary medical attention. (7)

The mainstays of therapy are fluid therapy, analgesics, and antivenom. Isotonic crystalloids are preferred for fluid resuscitation. (6) . Isotonic crystalloids are generally warranted at shock volume doses for the treatment of shock (6). After resuscitation, fluids are continued intravenously to account for maintenance needs and any ongoing losses.

Pain relief is likely warranted at presentation with caution exercised with drugs that may alter consciousness and confound interpretation of the patient's status. (6) Intravenous lidocaine and many opioids have been reported for pain relief, although, morphine should be used cautiously due to the potential risk of histamine release. (6)

Antivenom is the only proven specific therapy for envenomation. (7) Antivenom will reverse the hematologic and neurological effects of venom, but cannot reverse tissue necrosis. (6) Antivenom neutralizes toxin venom components limiting the spread of swelling, reversing coagulopathies, and stopping the progression of neuropathies. (9) Antivenom is more effective when given earlier, when the venom components are still in circulation. (7) Antivenom should optimally be given within 4 hours of envenomation, though it has been shown to be effective longer than 24 hours after. (9). Although antivenom may be beneficial in most cases, the absolute indications for administration are rapid progression of swelling, significant coagulation abnormalities, neuromuscular toxicity, and shock. (3) The average dose of antivenom in dogs and cats is 1 to 2 vials, but more may be needed and should be administered based on the patient's initial response to therapy (or lack thereof). (1) The dose of antivenom in smaller patients is higher per kilogram body weight. (1)

Antivenoms are composed of neutralizing antibodies that protect the recipient by passive immunization: the transfer of preformed antibodies from a donor to a recipient (9) The antibodies are made by hyperimmunizing a donor animal, a horse or sheep, then collecting plasma and extracting the fraction containing the antibodies. (9). There are two approved products in the U.S.; Antivenin Crotalidae Polyvalent (ACP) and Crofab Crotalinae Polyvalent Immune Fab (Crofab), which are equine and ovine derived, respectively. (6) The cheaper product, ACP, has been used in human medicine since 1954 (4) and is the only veterinary approved product (9). It is a whole IgG and horse albumin product, and is considered to be more antigenic. (4) Crofab is a newer ovine product made of a molecule called Fab, which is a cleaved portion of the IgG, making it smaller and less antigenic. (6) The disadvantages of this product are that the smaller molecule is more rapidly cleared from the body, the cost of the product, and that it is not veterinary approved. (9) Two products produced in Mexico and Costa Rica are considered effective, but are only available through acquisition of a special permit through the USDA. (6)

Antivenom has the propensity to cause reactions in the recipient animal due mostly to the inability to remove proteins other than IgG, such as albumin, alpha and beta globulins, and IgM during the purification process. Three reaction types are seen: anaphylaxis, delayed serum sickness, and anaphylactoid reaction. Anaphylaxis is rare but life threatening, and may be treated with epinephrine, glucocorticoids, H2 blockers, diphenhydramine, and fluid boluses (7). Early clinical signs of anaphylaxis are vomiting, salivation, restlessness, urticaria, and facial pruritis. (9) Delayed serum sickness is also rare in dogs compared to humans, likely due to the lower doses of antivenom administration in dogs compared to humans. (7) Clinical signs of serum sickness are fever, malaise, nausea, diarrhea, lymph node enlargement, and dermatopathy. (9) It generally occurs 3-14 days after antivenom administration. (9) Treatment is control of histamine

release with antihistamines and H2 blockers, and glucocorticoids. (7) The most common reaction seen is anaphylactoid reaction, which is a complement mediated reaction to rapid administration of antivenom. It is usually mitigated by stopping the infusion for 5 minutes and administering diphenhydramine, then restarting at a lower rate. (7)

Conditionally useful pharmacological therapies include antibiotics, antihistamines, and blood products. Though snakes have a diverse population of microbial organisms in their mouths, bacterial infections are rare and antibiotics are only indicated when there is tissue necrosis. (6) Antihistamines have no direct effects on venom, however antihistamines have been positively associated with survival in dogs. (3) Antihistamines are used during reactions to antivenom. Some amount of controversy surrounds the use of blood products in the snake bite victim due to the risk of transfusion reactions and ability to enhance abnormal thrombin formation (6). Whole blood is considered when Packed Cell Volume drops below 20% and clinical signs of anemia. (6) Fresh frozen plasma has been used to attempt to correct coagulopathies. Fresh frozen plasma will do little to correct coagulopathy without concurrent use of antivenom, therefore, it should be used if coagulopathy persists after adequate antivenom administration. (6)

Drugs to avoid using in snakebite treatment include synthetic colloids, non-steroidal anti-inflammatory drugs, heparin, steroids, and (previously mentioned) morphine. Synthetic colloids and NSAIDS have both been shown to impair platelet function, exacerbating venom induced coagulopathy. Furthermore, synthetic colloids can worsen interstitial edema and swelling if vasculitis is present and they escape the vasculature. (6) Corticosteroids have been shrouded in controversy for many years; though, the current recommendation is that steroids are not

indicated. (1) Many studies have shown no improvement or increases in mortality as well as possibly confounding laboratory measurements and impaired healing with steroid use. (1)

A vaccine exists to lessen the effects of North American rattlesnake envenomation, although, no peer reviewed studies exist on the efficacy of the vaccine. (1)

PROGNOSIS

Prognosis is dependent on bite severity and appropriate medical treatment. One study reported that increased number of vials of antivenom given was associated with worse outcomes, likely due to worse bite severity prompting more vials of antivenom to be given. (2) The same study found that administration of diphenhydramine and fluoroquinolones were associated with increased survival. (2) Mortality rates in dogs are 1-30% in comparison to the mortality rates in humans of <1% (6)

RESEARCH

The grave nature of snake envenomation, and the need for immediate treatment allow it to remain a significant area of study for veterinary practitioners. Few advancements have been made in the diagnosis and treatment of snake envenomation in recent years. Recent research pointed at the snakebite victim includes the use of thromboelastogram (TEG) to improve prognostic accuracy with venom induced coagulopathy. (10) A flat line tracing, or a decreased MA and G value at presentation were significantly associated with mortality. (10) Another area of clinical interest that is the subject of recent research is the use of low level laser therapy for crotalid induced myonecrosis. Initial indications are promising, but further research is warranted.

CONCLUSION

Crotalid envenomation is an important topic in veterinary medicine, especially in the South, due to frequency of envenomation and severity of clinical signs. The Crotalidae family is most frequently implicated in envenomation. (2) Often, history is suggestive but diagnosis is presumptive. (8) Clinical signs may be varied but localized swelling, hematologic abnormalities, venom induced coagulopathies, and hypovolemic shock are common. The mainstay of treatment is antivenom and supportive treatments such as fluids and analgesics.

RESOURCES

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