MoJo's Uh-Oh

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Introduction

Venomous snakebites in domestic animals is a serious problem in the United States, as there are estimated to be around 150,000 bites per year.[1,4] This is approximately 18 times more frequent than snakebite envenomation in humans.[6] Many reasons may influence this, the most common being increased amount of outdoor time with dogs and cats compared to humans, along with the decreased mental capacity of dogs and cats to perceive snakes as a threat.[6] There are two families of venomous snakes that are native to the United States, the Elapidae and Crotalidae. The Elapids consist of the coral snakes, and the Crotalids, also known as the pit vipers, consist of the rattlesnakes, water moccasins, and copperheads. The pit vipers are the largest group of venomous snakes in the United States and are responsible for approximately 99% of the venomous snake bites in dogs and cats.[1] This paper will focus on pit viper envenomation, more specifically water moccasin envenomation, in dogs.

The highest incidence of pit viper envenomation occurs in the southeast, western, and gulf coast states with approximately 90% of bites occurring from August to October, as snakes show increased aggression and venom yield with environmental warming and increased photoperiod.[1,3] Snake activity also increases during these months due to reproduction and egg hatching.[5] The water moccasins *(Agkistrodon piscivorus)*, also referred to as cottonmouths, black snakes, or black moccasins, are semi-aquatic snakes that are capable of biting while under water.[2] The name cottonmouth refers to the stark white interior of the snake's mouth that is often held open as a warning if it feels threatened.[13] Along with the other pit vipers, water moccasins have characteristic retractable front fangs, bilateral heat sensing "pits" between their nostrils and eyes, elliptical pupils, and triangular-shaped heads.[1] The majority of pit viper bites in dogs in the

United States are inflicted by rattlesnakes (65%), with copperhead (25%) and water moccasin (10%) bites occurring less frequently.[2,3]

Pit vipers can control the amount of venom they inject based on their perception of situations.[1] Bites are classified as dry, defensive, offensive or agonal. Dry bites comprise 25% of all pit viper bites and are non-envenomating.[2] Therefore, the appearance of fang marks does not mean that envenomation has occurred.[1] Defensive bites can either be non-envenomating or envenomating, though it is usually very small amounts of venom injected.[1,2] Pit vipers inject a controlled amount of venom with offensive bites and inject the entirety of their venom gland with agonal bites.[1,2] Due to a rather bellicose nature, water moccasins are more likely to envenomate when they strike.[1] Common signs of pit viper envenomation include pain, swelling, ecchymosis, weakness, sloughing tissue, shock, puncture wounds that ooze blood or serum, and nausea.[1,2]

Every species of pit viper's venom is of varying toxicity. Rattlesnakes have the most toxic venom, followed by water moccasins and copperheads, respectively.[1] However, there are many factors relating to the victim, the snake and the bite that determine the severity of envenomation.[2,3] The location, depth, and number of bites along with the victim's age, size, health status and time elapsed from bite to medical attention are all important factors.[2,3] Additionally, the size and age of the snake along with the quantity and toxicity of the venom injected all play a major role.[2,3]

History and Presentation

MoJo, a 3-year-old male neutered chocolate Labrador Retriever, presented to an emergency veterinary clinic on the Mississippi Gulf Coast on the evening of June 6, 2019, for a

snakebite to the muzzle. MoJo's owner was on the opposite side of their backyard and witnessed MoJo and his housemate attacking what appeared to be a large water moccasin. MoJo did not yelp or indicate that he was harmed in any way, so the owner was unaware that MoJo had been bitten until he approached the dogs and noticed two puncture marks on the right side of MoJo's muzzle. Swelling to the right side of the muzzle was rapid and progressed quickly to the right side of his neck which led MoJo's owner to promptly take him to the emergency clinic for further evaluation. MoJo and his family live next to a river, where water moccasins are frequently seen.

Upon presentation, MoJo was quiet, alert and responsive with a normal temperature of 102.2 degrees Fahrenheit and heart rate of 140 beats per minute. He was panting but was not dyspneic, and his mucous membranes were pink and moist with a capillary refill time of less than two seconds. His pupils were extremely dilated. Cardiopulmonary auscultation did not reveal any murmurs, arrhythmias, crackles or wheezes. There were two puncture wounds on the right side of his muzzle, approximately 3 centimeters apart from each other, that were oozing blood. Significant swelling was present on the right side of his muzzle and neck.

Pathophysiology

Pathophysiology of pit viper venom function is very multifaceted. The function of envenomation of prey is two-fold; immobilization and predigestion.[1,2] Complete digestion of non-envenomated prey can take up to 14 days.[2] With the injection of venom, digestion hastens to 2-5 days due to the complexity of the venom.[1,2] There are a multitude of enzymatic and nonenzymatic proteins that comprise snake venom and cause a variety of potentially life-threatening effects when injected into the dog or cat.[1,2,9]

Pit viper venom contains various myotoxins, cytotoxins, cardiotoxins, neurotoxins, and hemorrhagic toxins that can work collectively or individually.[5] When considering water moccasin envenomation, select myotoxins and hemorrhagic toxins frequently account for clinical signs. Myotoxins, such as hyaluronidase, collagenase, phospholipase A, and metalloproteinase are found in most pit viper venoms. The enzyme hyaluronidase, also known as the spreading factor, breaks down the viscosity of connective tissue by cleaving internal glycoside bonds and mucopolysaccharides which allows the venom to spread more rapidly.[2, 11] Another major enzyme involved is collagenase which breaks down collagen to allow for deeper penetration of the venom.[2,11] Phospholipase A damages sarcolemma and myocyte mitochondria, thus inducing myonecrosis by inhibiting cellular respiration, disrupting membranes, and uncoupling phosphorylation.[11,14] Phospholipase A can also release kinins, serotonin, and histamines which play a role in the progressive swelling and pain seen due to its ability to degrade membranes.[11] Venom metalloproteinases destroy extracellular matrix and basement membranes by releasing activated tumor necrosis factor alpha, a normal mediator of the inflammatory response.[2,11] Local tissue reactions are less significant with water moccasin and copperhead bites than with rattlesnakes.[2]

Coagulopathies are frequently seen with pit viper envenomation. The ability of venom to disrupt the coagulation process varies by species and ranges from inactivation of factors in the clotting cascade to the potential destruction of megakaryocytes in bone marrow and circulating blood.[1] A unique component of water moccasin venom is that it contains a protein C activator, which can act as an anti-coagulant by degrading factor V and VIII, and releasing a tissue-type plasminogen activator.[10,15] Fibrinolysis also occurs through interaction with plasminogen activator inhibitor.[15] Piscivorase I and II, both fibrinogenolytic enzymes, and applaggin and

piscivostatin, both disintegrins, also act as potent anti-coagulants. [10] These substances can work together to intensify the overall disruption of the clotting cascade.[10] Venom phospholipase A2 forms complexes with phospholipids, which are needed in the clotting cascade, and prevents them from being used, leading to a dysfunctional clotting cascade.[2]

Diagnostic Approach/Considerations

Appropriate primary and secondary triage examinations should be performed at initial presentation due to the rapid onset of most pit viper venoms and their ability to cause detrimental effects to different organ systems.[3,7] Primary triage examination should include evaluation of the cardiovascular system, the respiratory system, and a packed cell volume and total solids.[7] If possible, the area around puncture wounds should be shaved to assess for ecchymosis.[7]

A minimum database of complete blood count (CBC), chemistry panel with electrolytes, coagulation profile, and urinalysis should also be performed.[1-3] CBC abnormalities are usually non-specific and include anemia, leukocytosis, and thrombocytopenia.[2] Chemistry abnormalities can include but are not limited to an elevated creatine phosphokinase, hypokalemia, and azotemia.[2,5] A coagulation profile should include activated clotting time (ACT), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, fibrin degradation products, and an accurate platelet count, as clotting can be affected in many different ways.[2] Pigmenturia is common with snake envenomation and can be from hematuria, myoglobinuria or hemoglobinuria.[3] A blood smear can be performed to check for the presence of echinocytes which will be found in 89% of envenomated dogs within 24 hours. The presence of echinocytes is supportive but not definitively diagnostic for envenomation.[14] A unique adaptation from human medicine is the snakebite severity score. Utilization of this scoring system in veterinary

medicine can aid in determining if antivenom is necessary by evaluating severity, thus lessening the difficulty of monitoring envenomation progression.[2]

A CBC, chemistry panel with electrolytes and coagulation profile were performed on MoJo. CBC results were within normal limits, and the chemistry panel revealed a mildly decreased alkaline phosphatase (21 U/L; reference range 23-212) and cholesterol (101mg/dl; reference range 110-320). Prothrombin time (PT) was prolonged (>24 seconds; reference range 14-19) but activated partial thromboplastin time (aPTT) was within normal limits (93.4 seconds; reference range 75-105).

Treatment and Management

"The only proven specific therapy against pit viper envenomation is the administration of antivenin".[1] Without using the snakebite severity score, there are four indications for antivenin administration- rapid progression of swelling, neuromuscular toxicity, shock, and/or significant coagulopathy, defibrination or thrombocytopenia.[2] There are many different antivenin products available but their goal of neutralizing circulating venom components is the same.[4] MoJo received Rattler Antivenin, manufactured by Mg Biologics, which is an equine-derived plasma-based Crotalidae polyvalent antivenin that was released in 2017.[12] It contains antibodies collected from healthy horses immunized against the Western and Eastern Diamondback Rattlesnake, Prairie Rattlesnake, and Mohave Rattlesnake Type A.[8] It also supplements clotting factors and serum proteins. Rattler Antivenin is cross-protective and has been found to be effective against copperheads, water moccasins and other species of rattlesnakes.[8] For the first 24-48 hours after presentation, patient's vital parameters, along with assessment of coagulation

times and wound progression, should be serially monitored every 1-6 hours.[14] Additional antivenin may be necessary if patient's status and coagulation times worsen.[8]

Pit viper envenomation patients can be severely hypotensive and present in hypovolemic shock due to the pooling of blood within the shock organ, from fluid loss secondary to intense peripheral swelling, or from vasodilatory effects of the venom components.[1,2] Intravenous fluid therapy with crystalloids at appropriate doses for the patient is crucial to treat or prevent hypovolemic shock and to maintain perfusion.[14] Snakebites are usually very painful and proper analgesia should be administered at presentation.[2] NSAIDS are contraindicated if a coagulopathy is present due to impairment of platelet aggregation, which can worsen bleeding associated with venom-induced coagulopathy.[2,3] While venom is sterile, there are many different types of bacteria found in the mouth of snakes. Therefore, cleaning the puncture wounds, if able, along with broad-spectrum antimicrobial therapy is usually warranted, especially if evidence of tissue necrosis is already present.[1-3,7] Cryotherapy, hot packs, electroshock therapy, incision and suction of the bites, and applying tourniquets are contraindicated.[2]

Corticosteroid administration for treatment of snakebites is controversial. The mechanism of corticosteroids blocking phospholipase A, which is commonly found in snake venom, has led clinicians to believe steroids may be warranted.[16] However, numerous reports have documented different outcomes with the use of corticosteroids in snakebites. The different outcomes range from no effect on outcome to increased mortality, accentuation of the effects of venom, impairment of muscle regeneration, and interference with antivenom.[3] It is proposed that corticosteroids will inhibit the victim's natural defenses against venom and possibly distort diagnostic test results, making it more difficult to assess progression of envenomation.[1] Some

studies have shown a decrease in morbidity and mortality, however, these studies are from the 1960's.[3] Due to these findings, the use of corticosteroids is generally not recommended.[1]

An intravenous catheter was placed in MoJo's right cephalic vein, and lactated ringer solution was started at 120ml/hr (3ml/kg/hr; 1.5 times maintenance) to maintain perfusion. MoJo received an injection of dexamethasone sodium phosphate (4mg/ml, 0.25mg/kg, 2.4ml) intravenously at presentation and again 12 hours later due to rapid and progressive swelling from his muzzle to his neck. He also received an injection of buprenorphine (0.6mg/ml, 0.02mg/kg, 1.3ml) intravenously at presentation and again 8 hours later, along with cefazolin (1 gram/vial, 22mg/kg, 8.5 ml) intravenously every 8 hours, for three doses. MoJo was placed on oral gabapentin (600mg, 8mg/kg, ½ tablet q8-12h as needed), prednisone (20mg, 0.25mg/kg, ½ tab, 5 day tapering dose), and Clavamox (1000mg, 25mg/kg, 1 tablet q12h for 10 days) after receiving injectable drugs.

MoJo received one unit (50mls) of Rattler Antivenin which was given over one hour. The decision to administer antivenin was based upon the progressive swelling of MoJo's muzzle and neck along with the prolonged PT. The antivenin was given slowly over the first ten minutes and MoJo was monitored for signs of anaphylaxis including respiratory distress, vomiting, diarrhea, angioedema, and urticaria. No signs of anaphylaxis were noted, and the rate of antivenin administration was increased.

Case Outcome

MoJo's vital parameters were recorded four hours after antivenin administration and were found to be more normal than they were at presentation. Although his vital parameters never

exceeded normal limits at presentation, he was no longer panting, and his heart rate went from 140 bpm at presentation to 100 bpm. MoJo was seen resting comfortably prior to taking his vitals. He was offered a small amount of food at this time and ate all that was offered to him. MoJo's swelling gradually decreased the first night in hospital and was almost nonexistent at the time of discharge, 48 hours later. MoJo's owners were instructed to keep him indoors for rest for the next 3-5 days and to monitor him for any worsening of clinical signs. A recheck was said to be needed only if MoJo began to decline clinically. Mojo has two scars on his muzzle from the puncture wounds and luckily did not develop any tissue necrosis. His owner reports that he is doing well at home and has not had any more encounters with snakes.

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