NEWS FROM THE PIT

Arizona Poison and Drug Information Center

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Bleeding Out

Hemotoxicity from Rattlesnake Venom

By Tyler Hoelscher, MD

If I were to be a physician 200 years ago, my job would have been somewhat different. The prevailing belief at the time was that the body contained four substances, blood, phlegm, yellow bile, and black bile, and illness occurred when the balance of these four "humors" was altered. While I rarely worry about black bile in 2021, I still spend a substantial amount of my time trying to manage one of those humors: blood. Usually bleeding patients have had a traumatic injury, or are on medication to prevent their blood from clotting, but this is News from the Snake Pit, and so you can bet that we're going to talk about bleeding from snake bites.

NEWSLETTER HIGHLIGHTS

As we discussed in our last newsletter, hemotoxicity is one of the chief effects caused by rattlesnake envenomation. That prefix hemo- comes from the Greek word for blood, and what it specifically describes is the inability for blood to clot properly, the term we use for this phenomenon is coagulopathy. To understand treating the coagulopathy caused by rattlesnake venom you first must understand our bodies' natural clotting ability. I will oversimplify the process into two components: proteins and platelets. The protein side involves a nauseatingly complex series of interactions between proteins called clotting factors which ultimately cleave fibrinogen into fibrin (remember fibrinogen, you'll hear about it later), which forms a clot. The platelet side involves activating platelets (tiny cell fragments floating in your blood) which then become very sticky and aggregate together with the clot. When you get a papercut, these two branches work simultaneously to form a plug at the site of injury and stop the bleeding, thus exsanguination from papercuts is relatively rare. However, when these processes are interfered with, a minor bleed can become life threatening.

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Before we get back to snakes, let's look at one more thing, a syndrome called Disseminated Intravascular Coagulation (DIC). In DIC, platelets and the clotting cascade are inappropriately activated throughout the entire body. Platelets and clotting proteins are activated and form tiny clots called microthrombi which do no good to stop any bleeds, but use up the body's stored platelets and clotting factors. Once those are used up, the patient's blood is unable to properly clot and nurses will often notice blood oozing from small injuries, even from IV sites. Another helpful term here is "consumptive coagulopathy", the patient is coagulopathic i.e. their blood cannot clot, because the components in their blood used for clotting have been consumed. DIC is usually caused by a severe insult to the body, massive trauma, postpartum hemorrhage, extensive burns, sepsis, but the coagulopathy caused by a rattlesnake envenomation is very similar.

Rattlesnake venom contains a complex mixture of biomolecules, and among these are enzymes called proteases. These are proteins with catalytic functions that act as molecular scissors, cutting apart other proteins. Among these enzymes are a group called thrombin-like enzymes. Remember fibrinogen and fibrin? These thrombin-like enzymes cut fibrinogen into protein fragments unable to form clots. Other enzymes actually activate elements of the clotting cascade, which proceed to activate thrombin, which cleaves fibrinogen into fibrin, which is sticky and reactive, activating platelets and causing the creation of useless microthrombi like we see in DIC.

Other protein elements directly activate platelets, causing them to aggregate, and still other elements cause other cells in the blood and liver to sequester or to "eat" (phagocytose) those platelets. This and other similar processes cause a consumptive coagulopathy similar to DIC, which has been dubbed Venom Induced Consumptive Coagulopathy (VICC) which I will be going into more detail about in a later issue, but suffice to say, rattlesnake bite patients become coagulopathic, and it looks like DIC, but isn't true DIC.

When a patient is coagulopathic, they bleed a lot, no surprises there. There are two basic kinds of bleeding that happen to coagulopathic patients, provoked and spontaneous. Provoked bleeding is what we are all familiar with. When I skinned my knee a few weeks ago it bled a little bit. When a patient falls and breaks a bone you get a pocket of blood around the injury, called a hematoma. In coagulopathic patients a small cut or scrape might bleed for a lot longer than for a healthy patient, but as surgeons like to say, all bleeding must stop.

For that patient with the papercut it stopped because the body was able to salvage enough clotting factors to plug up the tiny bleed. Very commonly patients recovering from a rattlesnake envenomation will remark that minor injuries ooze blood for much longer than usual, but these are not a cause of significant concern. More concerning is when more significant trauma accompanies coagulopathy.

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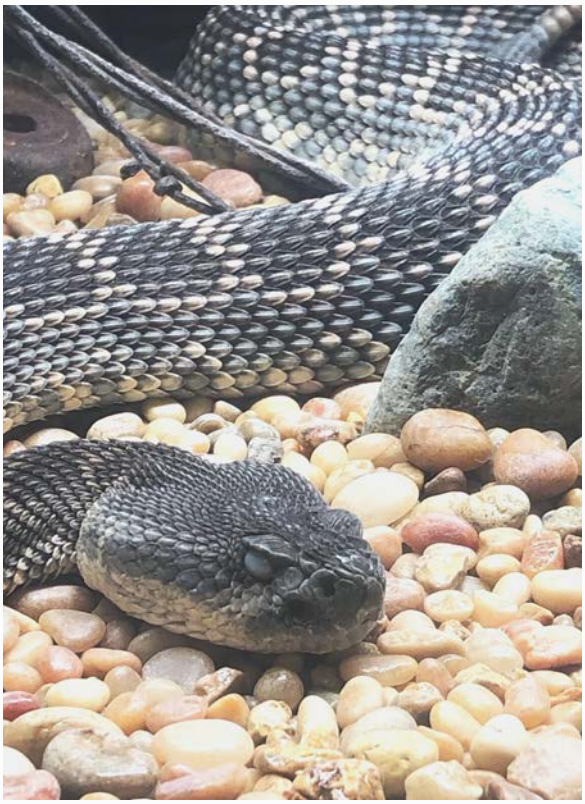
Snake fangs do not cause lacerations or punctures large enough to cause major bleeding, but occasionally a person will suffer a fall or other injury after they are struck by a snake, and if that fall causes bone fractures or injury to the body's soft tissues, significant bleeding can occur, and an otherwise minor to moderate injury will occasionally become very dangerous. One example of this is a patient who fell and broke a hip after being struck by a snake. This patient developed severe internal bleeding and required a procedure done by interventional radiology to seal the bleeding vessels. This is the same reason why we tell patients to avoid elective surgery and dental procedures for the few weeks following a rattlesnake envenomation.

The other group of bleeding patients are the ones we tend to worry the most about. When a person gets in a car accident and breaks a leg, you know to watch for bleeding. But what about when bleeding happens without any identifiable cause? What about when that bleeding is in a place you can't see? This group of bleeding patients have spontaneous bleeds, meaning we don't really know what makes them bleed. They may have had a minor trauma that they didn't notice or an underlying issue like a stomach ulcer that was primed to bleed given the right conditions. This bleeding usually happens in soft tissues and mucosa. By mucosa I mean the pink flesh you have inside your mouth and nose.

This is also found throughout the gastrointestinal (GI) tract and some genitourinary organs as well. Some mucosal bleeding is easy to recognize, like bleeding from the gums or the nose, or from the bladder causing bloody urine. Some can be more difficult though, bleeding in the GI tract will cause blood in the stool, but if this bleeding occurs in the stomach, the blood might be so digested that by the time it makes it into the toilet it's a deep black color that many people may not recognize as bleeding. When this goes unnoticed patients can become profoundly anemic before they start having other symptoms.

What about when bleeding is in a place you can't see?



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Some spontaneous bleeds also happen in other soft tissues. Bleeding into the arm or wrist is usually noticed when the arm becomes swollen and bruised, but we have also seen significant bleeding into the thigh that goes unnoticed. An adult's thigh can hold 1-2 liters of blood, and keep in mind that you have about 5 liters of blood so a large person can potentially lose 40% of their blood volume into their leg! There is also the fear that bleeding will occur in a closed compartment in the body as well, like the skull, for example.

Fortunately, significant bleeding after a snakebite tends to be quite rare. Over the last two decades we have seen a little less than 40 significant bleeds. Out of 2000 rattlesnake envenomations, that puts our rate of significant bleeding at about 2%. Minor bleeding is not always reported, so we're not exactly sure what those numbers are, but probably somewhere around 5%.Of the significant bleeds, about three-quarters, were spontaneous bleeds that happened without a clear cause. Also, worth noting, we have not had a recorded death caused by bleeding over these two decades, which speaks to the efficacy of our antivenoms, but may also be showing that we are probably worrying a little too much about bleeding in our rattlesnake bites.

There is a mantra in medicine, "Are you treating the numbers or the patient?" We very commonly see significant coagulopathies in our patients, their numbers look terrible, but the patient doesn't care about their laboratory values, they care if they bleed or not, and from the data we have, 98% of the time, there is no significant bleeding.

In the next letter I'll go over what it is we do for these bleeding patients when we see them, and how that has changed over the years. In the meantime, if you or your patient has been bitten by a snake, remember a toxicologist is never more than a phone call away at 1-800-222-1222.