Lack of Coagulopathy After Copperhead Snakebites

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Study objective: We determine the frequency and severity of abnormal laboratory measures of coagulation after suspected or known copperhead (*Agkistrodon contortrix*) envenomation.

Methods: We identified the charts of venomous snakebites in children presenting to St. Louis Children's Hospital over a period of time greater than 14 years and of all venomous snakebites in adults presenting to Barnes-Jewish Hospital over a period of time greater than 11 years. We identified all known or suspected copperhead snakebites. We excluded bites by rattlesnakes, cottonmouths, unidentified snakes, and captive or non-native snakes. We classified the confidence that the culprit was a copperhead snake as "positive" or "probable," according to the previously published criteria. We recorded the most extreme values for laboratory measures of coagulation for each patient.

Results: The final data set included 106 venomous snakebites, of which 45 were positively identified as attributable to copperheads and 61 probable copperheads. Results for international normalized ratio (INR), partial thromboplastin time (PTT), platelet count, and fibrinogen concentration remained within normal limits for 79%, 93%, 95%, and 91% of patients, respectively. The highest INRs and PTTs were 1.35 and 41 seconds, respectively, in different patients. Three patients had platelet counts below 100,000/mm^3 (54,000, 75,000, and 76,000/mm^3, respectively). The lowest fibrinogen concentration was 117 mg/dL. Five patients had 2 laboratory values outside normal ranges, and 1 had 3 abnormal laboratory values. No patient developed bleeding complications.

Conclusion: In identified copperhead snakebites, it may be safe to forgo serial coagulation testing in both adult and pediatric patients in the absence of clinical evidence of bleeding. [Ann Emerg Med. 2015;65:404-409.]

Please see page 405 for the Editor's Capsule Summary of this article.

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INTRODUCTION

The copperhead snake (*Agkistrodon contortrix*) is the most commonly reported snakebite. In 2012, US poison centers recorded 1,766 copperhead bites, of which 1,653 were treated in a medical facility.[1] There were another 670 bites from unknown crotaline snakes and 1,611 bites by other unidentified snakes. Together, these 3 categories accounted for 3,519 patients treated in health care facilities.

Copperhead snakes are native to the southeastern United States. Missouri has 2 subspecies of native copperheads, including the Osage copperhead (*A contortrix phaeogaster*), common in the northern two thirds of the state, and the southern copperhead (*A contortrix contortrix*), common in the Ozark Mountains in the southern third of the state.[2] Copperheads often reside close to or within human residential and recreational areas. Although not aggressive unless provoked, untoward contacts with humans are common. Because copperheads are the predominant venomous snake in our region, bites by unidentified snakes are likely to involve the copperhead snake.

Multiple clinical resources recommend routine CBC count, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and fibrin degradation products at initial presentation and again in 6 to 12 hours.[3-5] However, we rarely observe coagulopathy or clinical bleeding complications among patients with known or suspected copperhead bites.

We sought to determine the utility of such repeated laboratory measurements in both pediatric and adult patients who have presented to our medical center after suspected or known copperhead envenomation.

MATERIALS AND METHODS

We performed an institutional review board–approved, retrospective chart review of all venomous snakebites in children and adolescents presenting to St. Louis Children's Hospital between January 1, 1998, and August 24, 2012, and all venomous snakebites in adults presenting to Barnes-Jewish Hospital between May 1, 2001, and August 24, 2012. We identified potential cases by querying billing data for *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes for venomous snakebites and lizards E905.0, nonvenomous snakebites E906.2, or toxic effects of venom 989.5. Other sources of data to identify eligible charts included BJH Medical Records, Missouri Regional Poison Control

Editor's Capsule Summary

What is already known on this topic

Copperhead snakebites rarely cause coagulation abnormalities, but clinical guidelines often recommend measurement of coagulation studies.

What question this study addressed

Do abnormal laboratory measures of coagulation develop after copperhead snake envenomation?

What this study adds to our knowledge

In this 2-site retrospective review of 106 copperhead snakebites, coagulation study results remained within normal limits in most patients. The highest international normalized ratio was 1.35. Thrombocytopenia was present in 3 patients (lowest value 54,000/mm^3). No patient developed bleeding complications.

How this is relevant to clinical practice

Routine measurement of coagulation studies may not be needed for copperhead snakebites.

Center, and Washington University Toxicology Consult database. Sources of data for chart review included electronic medical records of emergency department (ED) and inpatient care. From the hospital charts, we recorded patient demographics; certainty of snake identification (positive, probable, or unknown); bite location on patient; laboratory coagulation values, including the most extreme values for each hospital visit; and clinical bleeding complications. We excluded bites by rattlesnakes, nonvenomous snakes, unidentified snakes, snakes not native to the region (such as exotic snakes kept by snake enthusiasts), and other animals.

We classified a snakebite as positive copperhead if the victim or bystander reported actually seeing the snake and was certain that it was a copperhead. Some of these patients arrived with the killed snake or occasionally with a photograph taken with a mobile telephone. We classified snakebite as probable copperhead if the bite occurred in an area known to have copperheads and if the victim or bystander expressed confidence that a copperhead was the culprit snake without certainty in visual identification. Some of these bites occurred in twilight or after sunset when snake color and markings were not easily seen. Our approach to classifying cases as positive or probable was similar to that used by Scharman and Noffsinger.[6]

We recorded data and calculated summary statistics in Excel 2010 (Microsoft, Redmond, WA) and imported the Excel file to JMP Pro (version 11; (SAS Institute, Inc., Cary, NC) for preparing figures. We did not assess interrater reliability within the study team because one team member (M.E.M.) was the consultant involved in the assessment and care of many of these patients.

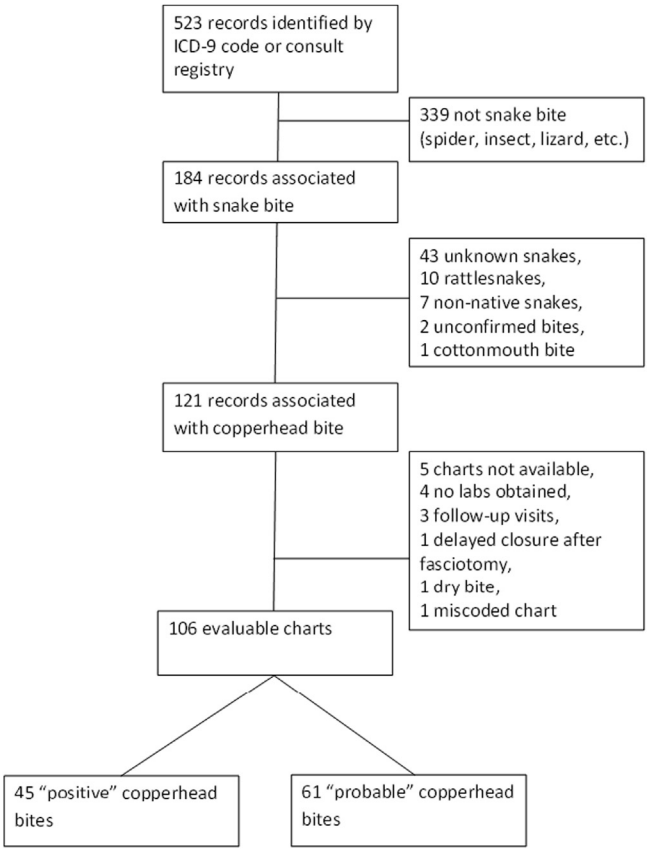

Figure 1. Algorithm for evaluation of snakebite medical records.

RESULTS

The initial search of *ICD-9* codes and our consulting registry yielded 523 records for screening. Of these, 106 charts met inclusion criteria and included 45 positive copperhead bites and 61 probable ones. Figure 1 shows the flow of included and excluded charts.

Median values for the most abnormal coagulation values among patients with positive copperhead bites were PT 13.7 seconds, PTT 31 seconds, international normalized ratio (INR) 1.1, platelet count 244,500/mm^3, and fibrinogen level 247.1 mg/dL. Median values for the most abnormal coagulation values among patients with probable copperhead bites were PT 14.1 seconds, PTT 29.3 seconds, INR 1.1, platelet count 246,600/mm^3, and fibrinogen level 279 mg/dL. Figure 2 shows medians, interquartile ranges, and outliers for the most extreme laboratory results.

One patient with abnormal results, an 8-year-old boy, was transferred from an outside hospital after a positive copperhead bite on the right middle finger. He had an initial platelet count of 293,000/mm^3 at the referring hospital, where he also received 4 vials of ovine-derived Fab antivenom (Crotalidae

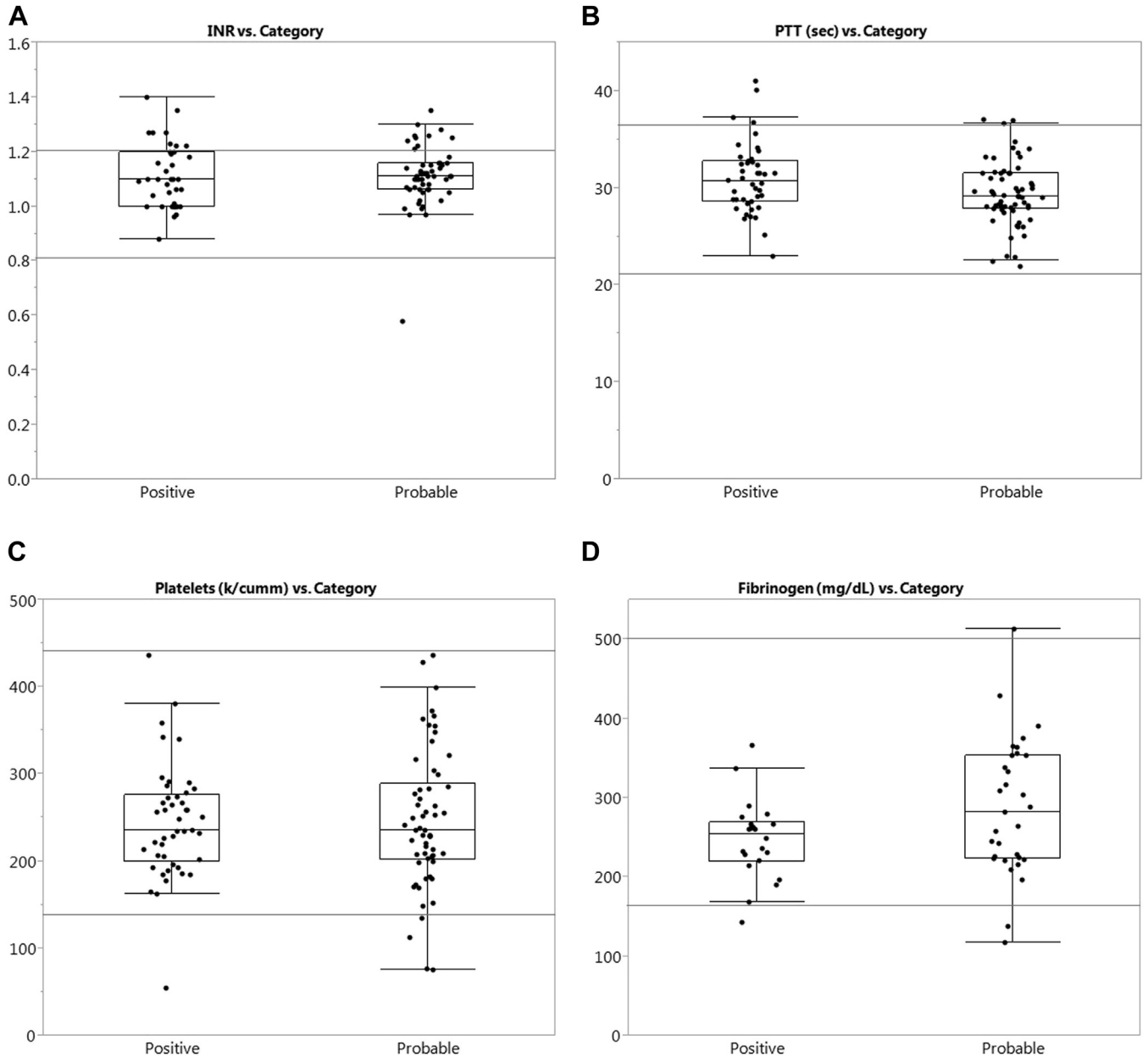

Figure 2. Box and whisker plot for *A*, INR; *B*, PTT; *C*, platelet count; and *D*, fibrinogen for patients with snakebites inflicted by snakes identified either positively or probably as copperheads. Boxes represent the interquartile range surrounding the median. The horizontal gray lines indicate the boundaries of the normal ranges (0.81 to 1.2 for INR, 21.0 to 36.5 seconds for PTT, 140,000 to 440,000/mm^3 for platelets, and 170 to 500 mg/dL for fibrinogen).

polyvalent immune Fab [ovine] [CroFab; FabAV]; BTG Pharmaceuticals, Conshohocken, PA) before transfer. His repeated platelet count on arrival to our hospital was 54,000/mm^3. Repeated laboratory testing within 10 hours showed a normal platelet count of 250,000/mm^3. The abnormal platelet count was believed to be an aberrant result because a pathologist reviewed the peripheral blood smear from this specimen and found no platelet clumping. His PT/INR and PTT were 12.5 seconds/1.0 and 31.5 seconds, respectively, at the referring hospital and 13.5 seconds/1.0 and 27.8 seconds, respectively, on arrival to our hospital. He had no bleeding complications, and his hemoglobin level remained normal (13.6 g/dL at the referring hospital, 12.3 g/dL at arrival to our hospital, and 13.1 g/dL 10 hours later. He received 2 additional vials of antivenom for pain and swelling.

Six patients had simultaneous abnormalities in 2 or more laboratory values (Table). All were slightly abnormal, with no observed bleeding complications. In no case did repeated coagulation values alter the clinical disposition of the patient.

Table. Laboratory values for 6 patients who had more than 1 abnormal coagulation test result.

Degree of Certainty	INR	PTT	Platelets	Fibrinogen
Positive	1.19	40.1*	219	168*
Presumptive	1.25*	36.6*	356	356
Presumptive	1.28*	28.1	76*	364
Presumptive	1.26*	27.7	112*	NA
Presumptive	1.25*	28.0	75*	138*
Presumptive	NA	37.1*	152	117*

NA, Missing values.
*Abnormal values. One missing INR occurred before our hospital reported INR with PT. For this patient, the PT was 14.2 seconds; the range of INR values for 5 other patients with the same PT was 1.02 to 1.21. Normal ranges were 0.81 to 1.20 for INR, 21.0 to 36.5 seconds for PTT, 140,000 to 440,000/mm^3 for platelets, and 170 to 500 mg/dL for fibrinogen.

LIMITATIONS

A limitation of our study is the reliance on the patient and bystanders for snake identification in most cases. Another limitation is that patients or bystanders may have overstated their confidence in snake identification or may have assumed that all biting snakes are copperheads. However, in some cases, the patient brought the killed snake to the ED or photographed it with a mobile telephone. In these cases, they accurately identified copperheads.

It is possible that the consistently normal laboratory values reflect adequate antivenom treatment, rather than a lack of coagulopathy. Seventy-five patients received at least 1 dose of FabAV. However, our findings appear consistent with published reports that preceded the Food and Drug Administration approval for FabAV.[6-9]

Another potential limitation of our study is that copperhead venom may vary with different subspecies or in different regions.[10] However, our results appear reasonably consistent with those of other published experiences in Missouri,[7] West Virginia,[6] Kentucky,[8] North Carolina,[9,11,12] Texas,[13-15] and Mississippi.[5]

DISCUSSION

Systemic coagulopathy and thrombocytopenia commonly occur after envenomations by rattlesnakes (*Crotalus* spp and *Sistrurus* spp) but appear to be uncommon with *Agkistrodon* envenomations. Patients with bites from North American pit vipers, including copperheads, are advised to undergo serial coagulation testing, regardless of geographic location or culprit species.[3-5] Our data suggest that copperhead envenomations may not require routine or repeated testing in the absence of clinically apparent bleeding.

Although copperhead snake venom contains fibrolase, a fibrinolytic enzyme,[16] serious bleeding complications and clinically significant laboratory abnormalities appear infrequently.[5-9,11-15]

Our results corroborate the observations of Anderson,[7] who in 1998 published his summary of 20 years' worth of copperhead snakebites in central Missouri. His experience preceded the availability of FabAV, and the horse serum–derived antivenom was seldom used for copperhead bites. Anderson stated, "Very little disturbance in homeostasis has been found in our experience with copperhead snake bites. Laboratory tests have not been remarkable."

Scharman and Noffsinger[6] retrospectively reviewed poison center records of patients with copperhead bites in West Virginia. Among the data that they collected were "laboratory findings" from reporting health care providers, although their study focused on grading severity of envenomation by local effects and did not include analysis of results of coagulation studies. Of 92 patients, 78% were admitted to the hospital, and 33% had local effect scores of 3 or 4 (on a scale from 0 to 4). They did not describe any bleeding complications or patients receiving transfusion, and they stated in their concluding paragraph that "systemic symptoms…were unusual occurrences."

White et al[8] reviewed snakebites reported to the Kentucky Regional Poison Center in 1 year. Of 26 cases, only 1 had "a slight elevation in…prothrombin time," and "all other laboratory values were within the normal range."

Garrison et al[13] specifically studied the occurrence of coagulopathy among 18 *A contortrix* envenomations in Texas; only 1 patient had abnormal laboratory values, including a maximum observed INR of 1.3 and PTT of 38.1 seconds. Both of these results are clinically insignificant.

Walker and Morrison[14] described their experience with 88 copperhead envenomations in east Texas. They stated that 10 patients "had elevated prothrombin times thought to be secondary to envenomation." They did not indicate the magnitude of these abnormal PT results, but they noted that "there were no cases of clinical bleeding." No patients received FabAV.

Correa et al[15] reviewed 151 pediatric snakebites, including 65 copperhead bites, managed at Texas Children's Hospital in Houston. Of 135 patients with laboratory studies after any snakebite, the authors observed that "the highest values for PT, INR, and PTT were 20.2, 1.6, and 40.6, respectively." No patient had a platelet count less than 100,000/mm^3. They concluded that "for copperhead and cottonmouth bites, it may be more appropriate to order laboratory studies only if significant envenomation is suspected by exam or the presence of systemic symptoms."

Thorson et al[9] reviewed 178 cases of copperhead bites in North Carolina and 2 neighboring counties in South Carolina. Two patients had clinically apparent bleeding. One was a toddler with multiple bites resulting in anemia that required transfusion; her PT and PTT results remained normal, at 13.4 and 25.5 seconds, respectively. The other was a man with severe systemic symptoms including hypotension with upper and lower gastrointestinal bleeding; his reported laboratory results included hemoglobin level 11.7 g/dL, PT 18.2 seconds, INR 2.1, PTT 49 seconds, platelet count 87,000/mm^3, and fibrinogen level 187 mg/dL. Ten other patients had elevated PT or PTT, and 2 had platelet counts between 87,000 and 148,000/mm^3 without overt bleeding.

Evans et al[12] studied the coagulation parameters in 94 patients with copperhead bites in North Carolina. Their most extreme

observed values were platelet count 96,000/mm^3, fibrinogen level 142 mg/dL, PT 14.1 seconds, and PTT 39.3 seconds. They similarly concluded that "routine hematologic tests to detect significant bleeding in all patients with copperhead snakebite…are not warranted."

Moriarty et al[5] reviewed their experience with 131 crotalid bites in Mississippi, including copperheads, cottonmouths, rattlesnakes, and unidentified snakes. They defined and analyzed coagulopathy as a dichotomous outcome according to whether any laboratory value was even slightly outside the reference range. This included a PT that was 0.1 second longer than the upper limit of 12.5 seconds and was classified as "positive coagulopathy." Most of the abnormal values deviated only slightly from the reference ranges and were not clinically significant. The only patient who had abnormal bleeding had a severe rattlesnake envenomation with hematemesis in the ED.

There is 1 unusual case report of coagulopathy (INR 4.23, PTT 80.6 seconds, fibrinogen level 39 mg/dL) rapidly following a confirmed copperhead bite with direct intravenous envenomation into the greater saphenous vein. He received 18 vials of FabAV and 8 units of fresh frozen plasma, with improvement during the next several hours.[17]

In an abstract, Weber et al[18] described a 35-year-old Missouri woman who reportedly injected a mixture of copperhead venom and methamphetamine. Although she developed fever, agitation, and hemoconcentration (hemoglobin level 19.1 g/dL), coagulation study results were described as "minimally elevated." Hospital treatment principally included intravenous fluids without antivenom. Her claim of acquiring and injecting copperhead venom could not be independently confirmed.

Mazer-Amirshahi et al[19] described a 17-month-old girl with copperhead bite to the foot, which resulted in swelling and ecchymosis up to the groin. Compartment pressure measurements indicated a compartment syndrome, which improved after a total of 26 vials of FabAV. The authors reported that she had no thrombocytopenia or coagulopathy during her 4 days in the hospital.

Lavonas et al[20] recently reviewed published cohort studies of North American pit viper envenomations to determine the frequency of medically significant late bleeding after treatment with FabAV. Of 1,107 patients included in the review, late bleeding occurred in only 9, of which 5 events were medically significant. Among their main results, the authors found that "no cases of late bleeding were reported after *Agkistrodon* envenomation."

In our study, systemic coagulopathy was not detected at presentation to the ED and did not develop during hospital admission. In snakebites identified as or presumed to be from copperheads, it is likely safe to forgo hospital admission for the purpose of serial coagulation testing in both adult and pediatric patients in the absence of clinically apparent bleeding. Our conclusions apply only to copperhead bites occurring in areas in which copperheads are endemic, not to envenomations by true rattlesnakes (*Crotalus* spp, *Sistrurus* spp), which have much greater propensity for coagulopathy and thrombocytopenia.

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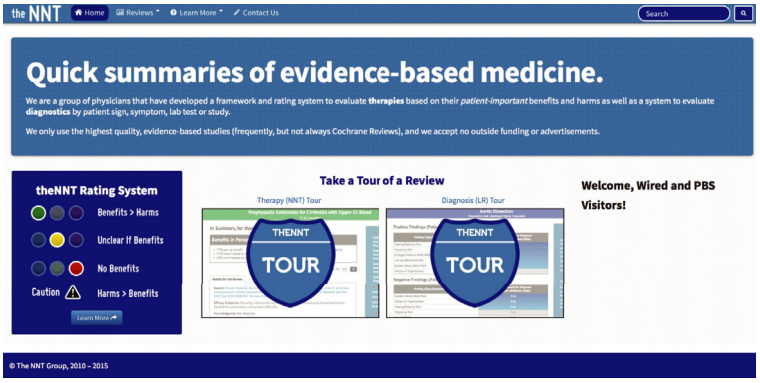
Links to Additional Resources



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