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Prospective evaluation of pain, swelling, and disability from copperhead envenomation

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ABSTRACT

Context: In light of the existing controversy regarding antivenin treatment for copperhead envenomation, a more detailed analysis of the disability from this species is needed. Objective: Our objective was to prospectively determine the duration of pain, swelling, and functional disability, i.e., residual venom effects, in patients with copperhead envenomation. Methods: Patients with venomous snakebite reported to the North Texas Poison Center between April 2009 and November 2011 were assessed. Patients with confirmed envenomations were contacted by a specialist in poison information. Day zero was the day of the bite and verbal phone consent for study enrollment was obtained at that time. The patient (or their guardian) was contacted by phone daily thereafter, and asked to rate their pain, edema/swelling, and disability using the modified DASH and LEFS scales. Patients were followed to resolution of all symptoms or return to baseline. Results: About 104 cases of venomous snakebite were followed; of which 17 were excluded due to being a dry bite (5) or for having insufficient data during follow-up (11) or due to coagulopathy (1). Overall, residual venom effects from copperhead bites for most patients last between 7 and 13 days. Median time to complete pain resolution was 7 days (mean = 10.7 days). Median length of time to resolution of swelling was 10 days (mean = 13 days) and median length of time to resolution of functional disability was 9 days (mean = 12.2 days). Discussion: Residual venom effects from copperhead envenomation in this study had a slightly shorter duration than some other studies. Data are skewed due to outliers where residual venom effects lasted for up to 89 days. Initial reoccurrence of some symptoms may be seen. Antivenom (AV) is currently being used for a large percentage of patients with copperhead envenomation. Finally, no differences in duration of venom effects were seen based on age or location of bite. Conclusion: Our study suggests that residual venom effects from copperhead species persist for between 10 and 13 days but may persist for months. Future studies are necessary to identify risk factors for severe/prolonged injury and to define the benefit of AV in patients with copperhead envenomation.

Discussion

Copperhead envenomations account for at least 35% of all snakebites reported to the US Poison Centers.[1] An internal review of snakebites for which a species was identified revealed that over 90% of snakebites reported to the North Texas Poison Center catchment area were from copperheads.[2] While the majority of envenomations from this species result in no more than localized pain and swelling,[3,4] the dramatic soft tissue swelling and the concern for more severe complications often motivates providers to administer antivenom (AV). An informed use of AV, however, requires a general understanding of the potential disability that may result from all bites. Previous studies done to define the copperhead related disability have either been retrospective in design,[5] prospective but included rattlesnakes bites,[4] or were limited by a small number of patients.[6] In addition, most previous studies were done at a time when only the equine-based AV was used. In light of the current controversy regarding AV therapy,[7] a detailed understanding of copperhead related morbidity of both the type of disability, and the duration of venom effects is needed.

Objective

Our objective was to prospectively describe the duration of pain, swelling, and disability, i.e., residual venom effects, in patients with copperhead envenomation.

Methods

Inclusion/exclusion criteria

Patients with venomous snakebite reported to the North Texas Poison Center (NTPC) between April 2009 and November 2011 were assessed prospectively for study eligibility. Patients unable or unwilling to follow-up by telephone were excluded. Bite day was deemed to be day 0 and verbal phone consent for study enrollment was obtained at that time. Dry bites were defined as bites that occurred without evidence of local tissue effects (other than puncture wounds) or systemic effects. Bites that were reported to be from rattlesnakes were excluded. Patients who could not be re-contacted, or for which three or more days of data could not be obtained were also excluded. Because hematologic venom effects are uncommon in...
copperhead victims [8] and because there is some overlap in with rattlesnakes in our region, patients who developed coagulopathy or thrombocytopenia were excluded.

**Data collection**

All poison specialists at the NTPC participated in the study and screened all potential snakebites as they were reported for inclusion. Prior to the study, Specialists in Poison Information (SPI) were educated about the use of a standard paper recording system (see Sample Data Tool; Appendix). The SPI read from a script informing the patient about the study and asked if they were willing to participate. Verbal phone consent for study enrollment was obtained on day zero. Participants were informed that they would be called on a daily basis by the poison center, at a contact number of their choice, and asked to rate their pain, swelling, and functional disability (see Assessment of Pain, Swelling, and Functional Disability below). Following discharge from the healthcare facility, SPIs performed daily telephone contact with the patients until resolution of all venom effects above. On those occasions, when contact could not be made, it was reattempted the following day and the entry for the day was left blank. For patients whose disability lasted >30 days, contacts were spaced out to every 3 days. In all cases, SPIs provided standard of care recommendations regarding snake envenomation management. Clinicians determined whether to use AV with the input of SPIs and toxicologists, but in many cases, AV was administered prior to poison center contact. Information regarding AV administered, complications of AV administration, and the need for surgery was collected while the patient was in the hospital based on a discussion with the patient provider. A waiver of written consent was granted by our institutional review board. No remuneration was provided to participants.

**Data analysis**

A database was generated using standard spreadsheet software (Excel®; Redmond, WA). Simple descriptive statistics were used for ordinal data analysis. Data were analyzed using Prism® software ver. 6 (San Diego, CA) to calculate the 25/75% interquartile ranges (IQR), and Pearson Skew coefficient (PSC). Hypothesis testing was neither planned nor performed.

**Snake identification**

Identification of the snake relied upon patient and provider reports. If reports were of an unknown species, in order to decrease the likelihood of including rattlesnake envenomations, envenomations were included only under the following conditions: (1) absence of coagulopathy or thrombocytopenia since coagulopathy is considered to be uncommon in copperhead envenomations [9] and (2) the bite occurred in the catchment area of the NTPC which overlaps the geographic area of predominantly copperhead habitat – see distribution in Poisonous Snakes of Texas.[10] Internal data from the Texas Poison Center database for years 2000–2014 for the NTPC catchment area revealed that 129/1523 (8%) of bites from identified snake envenomations are from rattlesnakes.[2]

**Assessment of pain, swelling, and functional disability**

The patient (or their guardian) was contacted by phone daily starting on day 1 and asked to rate their pain, using a Likert numeric scale of 0–10; limb swelling, and functional disability were classified as none, mild, moderate, or severe – (see appendix section). The definition of functional disability was determined using a modified DASH (Disability of Arm–Shoulder–Hand Questionnaire) [11] and LEFS (The Lower Extremity Functional Scale) [12] which have been validated in the setting of copperhead envenomation.[6] Follow-up was terminated on the first day the patient reported no pain (0/10), zero swelling, and no functional disability, i.e., complete resolution of all venom effects.

**Results**

About 104 patients were enrolled; 17 patients were excluded due to dry bites (5 patients with puncture wounds only) or due to incomplete data (12 patients with missing >3 days of follow-up data or coagulopathy) (Figure 1).

A total of 87 patients were included in the final analysis. Patients’ ages ranged from 2 to 79 years old with an average age of 35 years and standard deviation of 20 years. 58% (n=51) of patients were male and 42% were females (n = 36). 58% of bites occurred on lower extremity (LE) and 42% of bites occurred on upper extremity (UE) body parts. 66% (n = 57) of the patients received AV with an average dose of 8.4 vials. Snakes were positively identified by the patient or provider for 52 envenomations. The remaining 35 envenomations were presumed to be from copperheads based on the geographic location of bite and a lack of coagulopathy.

The length of time for pain, edema, and functional disability to resolve completely is shown in Figure 2. The data have skew reflecting the presence of outliers. Median time to complete pain resolution was 7 days (IQR: 4–12 days, PSC:+2.3 days, mean =10.7 days). Median length of time to resolution of swelling was 10 days (IQR: 6–16 days, PSC:+1.9 days, mean =13 days) and median length of time to resolution of functional disability was 9 days (IQR: 5–15 days, PSC:+3.5,
mean = 12.2 days). Figure 3 represents the time for resolution of any and all venom effects in all 87 patients. Figure 4 represents the time to resolution of symptoms and disability in patients who received AV (n = 57). Figure 5 describes the same for patients who did not receive AV. For those patients with symptoms lasting >20 days (n = 15), low levels of pain mirrored mild to moderate swelling and functional deficits until resolution.

Other outcomes included 5 allergic reactions to (2 anaphylactic – hypotension, and dyspnea; 1 urticarial, 2 unspecified), 1 minor procedure (bullectomy/lancing), and 1 cellulitis. Interestingly, several patients had initial resolution of pain but then experienced brief recurrences. Many had persistence of other venom effects despite resolution of pain.

Subgroup comparisons were made to show potential differences in resolution of venom effects by age, by location of bite, and based on whether the snake was identified (Figure 6). No major differences between groups were identified. A consistent trend toward longer disability in LE bites was observed, however, 95% confidence intervals (CIs) calculated for only this subset greatly overlapped (UE CIs for pain: 6–11 days; UE swelling CIs: 7–14 days, and LE swelling CIs: 8–12 days; UE dysfunction CIs: 6–11 days and LE dysfunction CIs: 8–11 days).
The differences in use of AV (11% in Spiller et al. versus 66% in rattlesnakes, or the spacing out of follow-up to longer intervals. may have been due to the Spiller's inclusion of more duration of disability seen in our study compared to Spiller's symptoms and only 9 patients received AV. The shorter patients were followed weekly, for the duration of their observations were from unidentified snakes. In the Spiller study, 81 identified as timber rattlesnakes. Seventeen of 81 envenomations were from copperheads. In our study, 30 patients received AV. In this study, patients were followed weekly, for the duration of their observation. The shorter patients were followed weekly, for the duration of their observation.

Scharman et al. [3] performed a retrospective evaluation of 92 copperhead snakebites in West Virginia and found that clinically significant effects (pain requiring parenteral analgesics, swelling, and ecchymosis of over one-half of the bitten extremity) occurred in 1/3 of patients. In this study, 8% of patients received AV. Duration of disability was, however, not discussed in Scharman’s study. The authors did emphasize, that ‘the generalization of copperhead snakebites as mild... should be reconsidered’.

Lavonas et al. [6] performed a prospective pilot study of recovery from copperhead envenomation, enrolling 20 patients. Follow-up was performed as an outpatient encounter on days 3, 7, 14, 21, and 28 with the goal of evaluating the utility of clinical outcome instruments (such as the DASH and LEFS). 75% of patients received AV. In this study, patients were grouped into mild (n = 1), moderate (n = 16), and severe (n = 3) envenomation groups based on severity of swelling instead of snakebite severity score. The authors concluded that signs, symptoms, impaired function, and decreased quality of life from copperhead envenomation typically last 7–14 days. This is similar to the duration of pain, swelling, and dysfunction reported in our group. They also state that residual signs and symptoms persisted in some subjects beyond the 28-day study predicted a steady increase in AV use in a later study. [13] Between 2006 and 2007, the reported incidence of AV use in Texas was 29% for all snake bites. The dramatic increase in AV administration identified in our study may be the result of toxicologist and SPIs becoming more comfortable recommending it, marketing, or litigation concerns. Clinicians also have more experience using it. Whether the trend of increasing AV use has any effect on disability is speculative. A multicenter trial is currently underway to determine AV effects for copperhead bites with mild to moderate venom effects. [14]

Another retrospective study by Thorson et al. [3] evaluated the type and extent of local reactions to copperhead bites. In this study, 178 cases were identified retrospectively from poison control records. Hospital records were reviewed in 25 cases, and follow-up calls were successful in 18 cases. Equine-derived AV was given in 8% (n = 14) of cases. In the 15 patients with mild-moderate envenomation, the median duration of limb dysfunction was 42 days with a range of 5–365 days, considerably longer than our study. While we cannot say with certainty the reason, our study does suggest a more benign clinical course. Thorson et al. may have included patients with more severe envenomation. In her study, hospital records identified 11 patients with coagulopathy that would have been excluded from our study. Other severe manifestations of envenomation described by Thorson included two patients who received blood products, six patients who required surgical debridement, two patients who required skin grafting, and one patient that required digit amputation. In our study, the most aggressive surgical procedure was a bullectomy. Follow-up was not as complete in the Thorson study as in ours suggesting the possibility of a selection bias in favor of the more severe cases. Geographical differences in snakes may have contributed to more severe envenomations. The skewed data in both studies again support the presence of outliers with more serious outcomes and delayed resolution of symptoms.

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observation period and that recovery may be slower for patients with LE envenomation. The duration of venom effects in the AV group were similar to the group that did not receive AV. However, this study was not designed to compare disability between these groups, and no claims regarding a benefit or lack of benefit from AV can be made. No statistical analyses were done to compare these two groups, and this study was not powered to find a difference. Groups who received AV were likely more severely envenomed which makes comparisons impossible. Ninety-five percent CIs for the UE versus LE were included to show that, even in the subgroup with a consistent trend, there would be no statistical difference. The end point of follow-up in this study was the day the patient reported zero pain, and no swelling, or functional deficits. Our data demonstrated that symptoms of pain and swelling frequently recurred with increased use of the affected extremity. Similar finding are reported by Spiller. This is not surprising since activity is likely to exacerbate injury in partially healed tissue. It does suggest that complete healing takes longer than patient’s first report of initial symptoms resolution. In all the patients, recurrent symptoms were fairly minor. Low levels of pain (1–3) and mild swelling often persisted for 1 month or more. Finally, differences in subgroups based on age or location of bite cannot be claimed, although there was a slight trend toward longer recovery in LE bites similar to Lavonas et al. study. If true this trend may be due to many factors including the reliance on the lower extremities for frequent mobility or biases that exist in the disability reporting tool. Since this study was designed to be descriptive, without pre-hoc power analysis on subgroups no statistical analysis were performed. Similarities in reported medians and means are noted.

Limitations
This prospective study relied on direct patient reporting of symptoms over the telephone and not a physical exam by a physician. Patient-reported outcomes have been advocated by the FDA as a preferred way to assess outcomes in clinical trials,[15] however, and follow-up was done on a daily basis with the same contact. The Likert pain scales used to define pain severity can be inconsistent, especially in patients who receive pain medication or are drug seeking. While poison specialists were trained in the use of the data collection tool no inter rater reliability testing was performed. Definitive snake identification is a weakness of this study and may have contributed to misinterpretation of disability if rattlesnakes were included. Excluding copperhead envenomations that did have coagulopathy may have resulted in a spectrum bias with the sampled population being less severely affected than the true population. This would have led to a shorter estimated time of disability in our study. Perhaps the greatest limitation of this study is that it is unable to assess the benefit of AV in treatment. This study was designed to be observational and no strong conclusions about subgroups can be made. Finally, disability of copperhead snakebite in Texas may not be generalizable to other parts of the country.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N</th>
<th>Time (days) to Pain Resolution (median/mean)</th>
<th>Time (days) to Swelling Resolution (median/mean)</th>
<th>Time (days) to Disability Resolution (median/mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-17</td>
<td>29</td>
<td>11 / 11.2</td>
<td>12 / 13.2</td>
<td>7 / 13.6</td>
</tr>
<tr>
<td>18-39</td>
<td>20</td>
<td>7.5 / 9.8</td>
<td>11.5 / 11.6</td>
<td>8.5 / 10.5</td>
</tr>
<tr>
<td>40+</td>
<td>38</td>
<td>8.5 / 11.2</td>
<td>10 / 14.1</td>
<td>10 / 12.6</td>
</tr>
<tr>
<td>All</td>
<td>87</td>
<td>7 / 10.7</td>
<td>10 / 13.0</td>
<td>9 / 12.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location of Bite</th>
<th>N</th>
<th>Time (days) to Pain Resolution (median/mean)</th>
<th>Time (days) to Swelling Resolution (median/mean)</th>
<th>Time (days) to Disability Resolution (median/mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Extremity</td>
<td>36</td>
<td>8 / 9.5</td>
<td>9 / 12.8</td>
<td>7 / 10.8</td>
</tr>
<tr>
<td>Lower Extremity</td>
<td>51</td>
<td>8 / 11.6</td>
<td>10 / 13.1</td>
<td>10 / 12.7</td>
</tr>
<tr>
<td>All</td>
<td>87</td>
<td>7 / 10.7</td>
<td>10 / 13.0</td>
<td>9 / 12.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Time (days) to Pain Resolution (median/mean)</th>
<th>Time (days) to Swelling Resolution (median/mean)</th>
<th>Time (days) to Disability Resolution (median/mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snake Identified as Copperhead</td>
<td>52</td>
<td>7 / 10.6</td>
<td>10 / 12.8</td>
<td>10 / 12.3</td>
</tr>
<tr>
<td>Snake not Identified</td>
<td>35</td>
<td>8 / 10.9</td>
<td>9 / 13.3</td>
<td>9 / 12.1</td>
</tr>
<tr>
<td>All</td>
<td>87</td>
<td>7 / 10.7</td>
<td>10 / 13.0</td>
<td>9 / 12.2</td>
</tr>
</tbody>
</table>

Figure 6. Subgroup comparison.
Summary

Overall, residual venom effects from copperhead bites for most patients last between 7 and 13 days. Median time to complete pain resolution was 7 days (mean = 10.7 days). Median length of time to resolution of swelling was 10 days (mean = 13 days) and median length of time to resolution of functional disability was 9 days (mean = 12.2 days). This is a shorter duration of injury than some previous studies have reported but consistent with the single recent study in which AV was used in a larger proportion of patients. Data were significantly skewed due to multiple outliers with prolonged effects lasting up to 89 days. No differences in duration of venom effects were seen based on age or location of bite. Future studies are needed to precisely define the benefit of AV in patients with copperhead envenomation and to identify those patients at risk for severe disability.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References


Appendix

Snake Bite Disability Tool

1. General Information:
   - Patient Age and Sex
   - Date of Bite
   - Location of Bite
   - Type of Snake if known
   - Type of Antivenom given
   - Number of vials of Antivenom given
   - Complications from Antivenom
   - Surgery?

2. Pain Assessment
   a. On a pain scale from 0-10 with 10 being the highest what is your current level of pain?

3. Swelling Assessment:
   a. Is the swelling arm, mild, moderate, or severe? (See definitions below)
      i. Minimal: Slight swelling just around the bite
      ii. Mild Swelling: less than 2 inches (5 cm) or not extending beyond a major joint, i.e., the hand to forearm (over wrist), or from the forearm to the arm (past elbow).
      iii. Moderate Swelling: More than 2 inches (5 cm) but less than 4 inches (10 cm) or extending beyond a major joint, i.e., from the hand to forearm (over wrist), or from the forearm to the arm (past elbow).
      iv. Severe Swelling: More than 4 inches (10 cm)

4. Functional Assessment:
   a. Is there no, mild, moderate, or severe functional deficit? (See definitions below)
      i. Mild deficit:
         1. Foot/ Leg/ Thigh: Able to walk 2 blocks with mild pain
         2. Hand/ Forearm/ Head: Able to eat, cut food
      ii. Moderate deficit:
         1. Foot/ Leg/ Thigh: Can weight bear for quick trips to the bathroom, TV, etc. – not out of the house
         2. Hand/ Forearm/ Head: Able to eat, cut food. Able to carry drinks, groceries, light objects
      iii. Severe deficit: Unable to use extremity for any function
         1. Foot/ Leg/ Thigh: No walking, but nor
         2. Hand/ Forearm/ Head: unable to carry objects or use arm

5. General Comments (Please comment on any relevant extenuating or unusual circumstances regarding this case):