Clinical Presentation and Outcomes Associated with Different Treatment Modalities for Pediatric Bark Scorpion Envenomation

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Abstract

Introduction Scorpion envenomation is potentially life-threatening and affects children in the Southwestern USA. An FDA-approved antivenom is available, but its high cost has led to use of off-label antivenom dosing or supportive care alone as alternatives to FDA-recommended dosing. This study sought to determine whether treatment approach influences outcomes in envenomated children.

Methods A retrospective cohort study of children with grade III or IV scorpion envenomation evaluated in Phoenix Children's Hospital ED between September 1, 2011, and March 31, 2014. Patients were grouped based on treatment: group 1, supportive care only; group 2, FDA-recommended dosing (3-vial initial dose); group 3, "off label" dosing (1–2 vial initial dose). Primary outcomes were ED length of stay and hospital admission. Secondary outcomes were mechanical ventilation and aspiration pneumonia.

Results One hundred fifty-six patients were included with 58 patients in group 1, 16 patients in group 2, and 82 patients in group 3. Group 1 was significantly older than the antivenom groups ($p < 0.001$), and group 2 was younger than group 3 ($p = 0.024$). Envenomation grade was also different, with group

1 having fewer grade IV than groups 2 and 3 ($p < 0.001$). Three percent of group 1, 56 % of group 2, and 28 % of group 3 had respiratory distress ($p < 0.001$). ED LOS was not significantly different between groups. Hospital admission occurred in 3.4 % group 1, no group 2, and 8.5 % group 3 patients. Two intubations and two aspirations occurred in group 3.

Conclusions In this study, clinical presentation appeared to influence treatment. Groups that received antivenom had a higher envenomation grade than the group that received supportive care. The FDA-recommended dosing group was younger and had more respiratory distress than those treated with initial doses of 1–2 vials. Outcomes were not significantly different between groups. Prospective studies may identify the ideal population for each treatment approach.

Keywords Scorpion · Envenomation · Antivenom · Anascorp · Centruroides

Introduction

Envenomation by *Centruroides sculpturatus* (bark scorpion) can lead to serious and potentially life-threatening illness in young children in the Southwestern USA. Symptoms can range from localized pain to cranial nerve dysfunction and/or neuromuscular hyperactivity [1]. The severity of envenomation is graded from I–IV based on symptoms. Mild envenomation is given a grade of I or II and involves pain and paresthesias at the sting site or at a remote site. Grade III or IV envenomation presents with cranial nerve or somatic skeletal neuromuscular dysfunction or with both, respectively [2]. Severe envenomation can lead to excessive salivation, stridor, loss of pharyngeal muscle control, difficulty swallowing, and respiratory failure [3].

In 2011, the first FDA-approved scorpion antivenom, Centruroides (Scorpion) Immune F(ab')₂ (Equine) Injection

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(Anascorp®), became available for use in patients presenting to the emergency department with grade III or IV scorpion envenomation. The initial dose recommendation is three vials as per the package insert instructions. Subsequent one-vial doses are recommended if symptoms do not resolve after a 30–60-min observation period [4]. A randomized, double-blinded placebo-controlled trial of 15 patients showed complete resolution of all 8 patients who received the antivenom within 4 h of administration versus 1 of 7 patients who received placebo [5]. Anascorp® use has been shown to be safe and effective and has allowed affected patients to be discharged from the emergency department with resolution of symptoms [6].

Prior to the availability of antivenom, supportive care measures were used to treat scorpion envenomation. Common pharmacologic treatment includes benzodiazepine and opioid administration to control agitation and pain [7, 8]. With only supportive care, patients often require admission to the ICU and mechanical ventilation [7]. The use of antivenom, however, has allowed patients to be discharged directly from the emergency department [6].

Due to the high cost of the antivenom (\$3750/vial), some hospitals have adopted guidelines recommending physicians to use a single-vial initial dose of antivenom rather than three vials. In addition, some physicians and families are choosing not to use the antivenom and instead provide traditional supportive care to patients [9]. At Phoenix Children's Hospital, such guidelines were developed after approval of Anascorp® but the final decision regarding whether to use antivenom and what dose to administer was at the discretion of the treating emergency physician. The purpose of this study is to determine whether treatment approach influences emergency department (ED) length of stay (LOS), hospital admission rate, and complications in children with grade III or IV bark scorpion envenomation.

Methods

This is a retrospective cohort study of all patients presenting to Phoenix Children's Hospital (PCH) Emergency Department between September 1, 2011, and March 31, 2014, with grade III or IV scorpion envenomation. The study was approved by the PCH Investigational Review Board. Subjects were identified through a search of ICD-9 code 989.5 (toxic effect of venom) or E905.2 (scorpion sting causing poisoning). A preliminary review of charts was completed to identify patients documented as having a grade III or grade IV scorpion envenomation for inclusion in the study. Only patients ≤ 18 years of age who presented directly to the ED, or those who were transferred from an outside hospital to the ED were included. Patients were included only if signs of grade III or IV envenomation were noted during PCH ED evaluation. If reference was made to earlier grade III or IV signs, but these were not noted on presentation to the PCH ED, the patient was excluded. Patients with a grade I

or II scorpion envenomation or those found to have an alternative diagnosis were excluded. In addition, patients who received Anascorp® from an outside hospital prior to transfer to the ED at Phoenix Children's Hospital were excluded.

The charts of patients who met inclusion criteria were reviewed, with data extracted to a standardized data collection form by two investigators and then entered into an Excel spreadsheet. The investigators underwent a training session in data abstraction prior to chart review, and 10 % of the charts were reviewed by two investigators to calculate a kappa statistic to determine inter-rater reliability. Data included age, weight, sex, time from sting to PCH ED, clinical findings, treatment, admission, and PCH ED length of stay. Symptoms were classified as cranial nerve abnormalities, neuromuscular symptoms, and respiratory distress. Patients were placed in one of three groups based on treatment received. Group 1 patients received supportive care only with no antivenom given. Group 2 patients received Anascorp® based on FDA dosing (3 vials as the initial dose). Group 3 included patients who received Anascorp® as non-FDA dose scheduling (1 or 2 vials as the initial dose). Primary outcomes were PCH ED LOS and admission to the hospital. Secondary outcomes were rates of clinical complications including respiratory failure requiring mechanical ventilation and aspiration pneumonia.

Descriptive statistics were used to describe the overall outcomes and outcomes stratified by group. Continuous variables were reported as means and standard deviations for normally distributed variables and as medians and IQR's for non-normal variables. Categorical variables were reported as *N* and percentage. Chi-squared analysis were performed to compare categorical outcomes (hospital admission, clinical complications) between groups. ANOVA was performed to compare continuous outcomes. A two-tailed $p < 0.05$ was considered significant.

Results

There were 332 patients who were evaluated in the PCH ED with a diagnosis of scorpion envenomation between September 1, 2011, and March 31, 2014. Of these patients, 160 (48.2 %) had findings consistent with grade III or IV envenomation. An additional four patients (1.2 %) were excluded due to treatment with Anascorp® at an outside hospital prior to transfer to PCH ED.

Sixteen randomly selected charts were chosen to evaluate inter-observer reliability. Two of the authors independently extracted the variables respiratory distress, neuromuscular findings, cranial nerve involvement, time from sting to PCH ED, and ED LOS. For the last two variables, agreement was defined as one rater recording a value that was ± 30 min of the other rater. The percent agreement was 100 % for all but respiratory distress (93.8 %). Kappa scores could be calculated

for the first three variables and were 0.88 for respiratory distress and 1.0 for the other two.

A total of 156 patients were included in this study with 42 (27 %) grade III and 114 (73 %) grade IV envenomations. Seventy-three (21.8 %) patients had respiratory distress documented. The characteristics of each group are found in Table 1. Patients were not evenly distributed between groups and baseline characteristics of groups were different. There were 58 patients in group 1 (41 % grade IV), 16 patients in group 2 (87 % grade IV), and 82 patients in group 3 (93 % grade IV). Patients in group 1 were older than patients in group 2 and group 3 ($p < 0.001$), while patients in group 2 were younger than those in group 3 ($p = 0.024$). There was also a significant difference in the envenomation grade between groups, with group 1 having fewer grade IV subjects than group 2 and group 3 ($p < 0.001$). Respiratory distress was documented in only 3 % of patients in group 1, but in 56 % of patients in group 2, and 28 % in group 3 ($p < 0.001$). The times from the initial envenomation to presentation to the PCH ED were similar between groups.

A total of 98 (62.8 %) patients received antivenom. In group 3, the group with sequential vial dosing, 44 patients (54 %) received a total of two vials while 28 patients (34 %) received only one vial. One patient received five vials which was the maximum number of vials given to a patient in this study. Group 2 patients, who were given an initial three-vial dose, received more vials compared to group 3. The median total vials given in group 2 was 3.0 while group 3 patients were given a median of 2.0 vials ($p < 0.001$).

The outcomes are summarized in Table 2. The primary outcome parameter, PCH ED LOS, was not significantly different between groups. The other primary outcome, admission to the hospital, occurred in 3.4 % of group 1 subjects, no group 2 subjects, and 8.5 % of group 3 subjects. Hospital admission lasted 24–36 h in 5 patients, 12–24 h in 3 patients, and 84–96 h in one 18-month-old patient with multiple co-morbidities

Table 2 Outcomes

	Group 1	Group 2	Group 3	<i>p</i> value
ED length of stay (min)	261 (128)	253 (72)	259 (114)	0.839
Hospitalization	2 (3.4 %)	0 %	7 (8.5 %)	0.167
Intubation	0 %	0 %	2 (2.4 %)	0.607
Aspiration	0 %	0 %	2 (2.4 %)	0.607

Group 1, no antivenom; group 2, dosing per FDA guidelines; group 3, “off-label” antivenom dosing

due to premature birth. We were unable to find significant differences between groups. Two patients were intubated and two patients had aspirations, both in group 3. One patient was 12 months old who presented to the PCH ED with respiratory distress, stridor, and oxygen saturation in the 80s. One vial of antivenom was initiated, but oxygenation worsened and ventilation using bag valve mask was ineffective due to laryngospasm and emesis. The child was intubated and there was no evidence of aspiration on chest radiograph. The second intubated patient was a 4-year old who presented with excessive secretions and low oxygen saturation. Lorazepam and fentanyl were administered, and one vial of antivenom was initiated. Oxygen saturation fell below 80 % and laryngospasm prevented bag valve mask ventilation. Chest radiograph revealed aspiration. The second case of aspiration occurred in a 4-year-old patient with a history of premature birth and chronic lung disease. Chest radiograph revealed aspiration and continued oxygen requirement necessitated hospital admission. There were no deaths in the study population.

Discussion

Envenomation by *C. sculpturatus* can produce significant illness in children in the Southwestern USA. Clinical findings

Table 1 Baseline characteristics of patients and treatment approach

	Total	Group 1	Group 2	Group 3	<i>p</i> value
# of patients	156	58 (37.2 %)	16 (10.3 %)	82 (52.6 %)	
Median age ^a (IQR)	3.0 (1.9, 6.0)	5.0 (2.4–8.0)	2.0 (1.0–3.0)	3.0 (1.8–5.3)	0.001 ^b 0.024 ^c
Boys	90 (57.7 %)	30 (51.7 %)	10 (62.5 %)	51 (62.1 %)	
Median time to ED (IQR) ^d	125 (60.3, 228.0)	158 (60–296)	120 (65–223)	122 (60–191)	0.153
Grade IV	114 (73.1 %)	24 (41.4 %)	14 (87.5 %)	76 (92.6 %)	<0.001 ^b
Respiratory distress	34 (21.8 %)	2 (3.4 %)	9 (56.3 %)	23 (28.0 %)	<0.001 ^b <0.041 ^c
Median # vials		0	3.0 (3.0–3.8)	2.0 (1.0–2.0)	<0.001 ^c

^a Age in years

^b For group 1 vs. groups 2 and 3

^c For group 2 vs. group 3

^d Time in minutes from envenomation to PCH ED

associated with grades III and IV envenomations are often serious enough to necessitate medical intervention with opioids, benzodiazepines, airway support, or antivenom. Grade IV envenomation is the most severe category of envenomation, but within this grade, there may be a wide spectrum of illness severity, with milder cases exhibiting only subtle muscle tremors and nystagmus while the most severe cases may have neuromuscular agitation, hyperadrenergic state, and respiratory failure. The conventional grading system does not discriminate severity of illness within grade IV.

Prior to 2004, an anti-*Centruroides* whole IgG antivenom was available for use only in the state of Arizona. Although this reduced hospitalization, it was associated with anaphylaxis and delayed hypersensitivity. Due to the risks, some clinicians chose to use supportive care instead [10]. After this antivenom became unavailable, intensive care admissions for scorpion envenomation considerably increased with one study reporting a nearly 500 % increase in admissions over baseline [11]. Since Anascorp® has been available, hospitalization rates are again low. Nine (5.8 %) patients of 156 in this study were hospitalized, with only three children admitted to the intensive care unit.

Perhaps the most remarkable finding of this study is that the ED LOS was similar between the groups that received antivenom and the group that was not treated with antivenom. This finding, together with the baseline differences between groups, strongly suggests that PCH emergency physicians tailor their treatment based on severity of clinical presentation and/or perceived risk for deterioration. Group 1 patients, who received only supportive care, were less ill on presentation, with less than half of patients meeting grade IV criteria. Children in this group were older and only 3 % had respiratory distress. The mean ED LOS of 261 min in this group, while similar to the other treatment groups in this study, differs greatly from the LOS of 28.7 h that was reported in a previous pediatric scorpion envenomation cohort presenting to PCH when antivenom was unavailable [7]. This comparison highlights the relative mild severity of illness of children in group 1. It appears that the treating physicians assessed these patients to be in less need of a high-cost antidotal treatment and chose supportive care.

Severity of illness at presentation also appears to have influenced the dosing regimen when the decision to administer antivenom was made. Group 2 patients, who received three vials as the initial dose, as recommended in the Anascorp® package insert, were significantly younger, and greater than half had respiratory distress. Despite being at highest risk for hospital admission and complications based on these characteristics, there were no admissions, intubations, or aspirations in this group.

More than half of the patients in this study received off-label dosing of antivenom, making group 3 the largest group. Nearly all patients in this group had grade IV envenomations,

and nearly a third presented with respiratory distress. Most patients were discharged home from the ED, with the same ED LOS as group 2 patients. However, almost all of the hospitalizations that occurred in this study, and the three patients with intubations and/or aspirations, were in this group. This could be considered a treatment failure since a main objective for using scorpion antivenom is to avoid hospital admission. Reasons for hospital admission in patients who are treated with antivenom may include aspiration, residual effects of benzodiazepines given to control agitation while administering sequential antivenom doses, or residual envenomation effects when suboptimal doses of antivenom are used. The latter scenario might occur when physicians decide symptoms are no longer severe enough to warrant more antivenom but are unable to discharge the patient home due to residual envenomation effects. Comparisons of these secondary outcomes cannot be made between the antivenom groups due to the small number of patients in group 2. A prospective dosing study would be helpful to determine if sequential single vial dosing results in different hospital admission rates or complications than an initial three-vial dose. Based on our results, it appears that single sequential vial dosing results in a good outcome in most patients, but it is unclear which patients are most appropriate for this treatment approach and if there are certain patients in whom this approach should be avoided, such as those who are younger or with more severe presentations.

Limitations of this study include the retrospective study design. If clinical effects were present but not documented, this may have affected results. We used PCH ED LOS as an outcome due to the lack of documentation of the exact time when symptoms resolved. External factors such as physician or nursing availability could have potentially caused delays in discharge. Patients met discharge criteria when they were awake, alert, and tolerating oral intake. Symptoms of envenomation may have resolved, but LOS may be prolonged due to a child's willingness to eat or drink. Another limitation is that there was no documentation as to why physicians chose a particular treatment approach. Our results suggest severity of illness influenced choice of treatment, but specific physicians may have chosen to follow FDA recommendations as opposed to hospital guidelines, regardless of illness severity or vice versa. We did not include time spent in a different ED prior to transfer as part of ED LOS. Patients with scorpion envenomation are often transferred to the PCH ED from EDs that do not stock antivenom or that do not have pediatric services. Prior to transfer, patients may receive treatments such as benzodiazepines and opioids. These medications do not reverse envenomation and are unlikely to have affected eligibility for our study, although it is possible. Time spent in other EDs prior to transfer is also unlikely to have affected our results, as time from envenomation to arrival in PCH ED was similar between groups. However, some patients who

presented to other EDs with grade III or IV findings may have arrived to PCH with resolution of these findings and thus not been included. This study was also limited by the differences in numbers of patients between groups, limiting our ability to detect differences if they were present.

Conclusions

In this study comparing outcomes in children with scorpion envenomation after FDA-approval of anti-*Centruroides* antivenom, clinical presentation appeared to influence treatment approach. The groups of patients that received antivenom had a higher envenomation grade than the group that received supportive care. Patients who were treated with an initial three-vial dose of antivenom were younger and had more respiratory distress than those who were treated with initial doses of one or two vials. There were no significant differences in outcomes between groups. Prospective studies may help identify the ideal population for each treatment approach and determine if there are differences in admission and complication rates with different dosing regimens.

Compliance with Ethical Standards

Conflicts of Interest None of the authors have any conflicting financial relationships to declare.

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References

1. LoVecchio F, McBride C. Scorpion envenomations in young children in Central Arizona. *J Toxicol Clin Toxicol.* 2003;41(7):937–40.
2. Curry SC, Vance MV, Ryan PJ, Kunkel DB, Northey WT. Envenomation by the scorpion *Centruroides sculpturatus*. *J Toxicol Clin Toxicol.* 1983-1984;21(4–5):417–49.
3. Skolnik AB, Ewald MB. Pediatric scorpion envenomation in the United States: morbidity, mortality, and therapeutic innovations. *Pediatr Emerg Care.* 2013;29(1):98–103.
4. US Food and Drug Administration: Anascorp® package insert. Available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM266725.pdf>
5. Boyer LV, Theodorou AA, Berg RA, Mallie J. Antivenom for critically ill children with neurotoxicity from scorpion stings. *N Engl J Med.* 2009;360:2090–8.
6. Boyer L, Degan J, Ruha AM, et al. Safety of intravenous equine F(ab')₂: insights following clinical trials involving 1534 recipients of scorpion antivenom. *Toxicon.* 2013;76:386–93.
7. O'Connor A, Ruha AM. Clinical course of bark scorpion envenomation managed without antivenom. *J Med Toxicol.* 2012;8(3):258–62.
8. Gibly R, Williams M, Walter FG, McNally J, Conroy C, Berg RA. Continuous intravenous midazolam infusion for *Centruroides exilicauda* scorpion envenomation. *Ann Emerg Med.* 1999;34(5):620–5.
9. Armstrong EP, Bakall M, Skrepnek GH, Boyer LV. Is scorpion antivenom cost-effective as marketed in the United States? *Toxicon.* 2013;76:394–8.
10. Bond GR. Antivenin administration for *Centruroides* scorpion sting: risks and benefits. *Ann Emerg Med.* 1992;21(7):788–91.
11. Riley BD, LoVecchio F, Pizon AF. Lack of scorpion antivenom leads to increased pediatric ICU admissions. *Ann Emerg Med.* 2006;47(4):398–9.