Comparison of Antivenom Dosing Strategies for Rattlesnake Envenomation

Meghan B. Spyres, MD[1]; Aaron B. Skolnik, MD[2]; Elizabeth C. Moore, DO[1]; Richard D. Gerkin, MD[3,4]; Angela Padilla-Jones, RN[3]; Anne-Michelle Ruha, MD[3,4]

Objectives: This study compares maintenance with clinical- and laboratory-triggered (as-needed [PRN]) antivenom dosing strategies with regard to patient-centered outcomes after rattlesnake envenomation.

Design: This is a retrospective cohort study of adult rattlesnake envenomations treated at a regional toxicology center. Data on demographics, envenomation details, antivenom administration, length of stay, and laboratory and clinical outcomes were compared between the PRN and maintenance groups. Primary outcomes were hospital length of stay and total antivenom used, with a hypothesis of no difference between the two dosing strategies.

Setting: A single regional toxicology center

Patients: Three-hundred ten adult patients envenomated by rattlesnakes between 2007 and 2014 were included. Patients were excluded if no antivenom was administered or for receiving an antivenom other than Crofab (BTG International, West Conshohocken, PA).

Interventions: This is a retrospective study of rattlesnake envenomations treated with and without maintenance antivenom dosing.

Main Results: One-hundred forty-eight in the maintenance group and 162 in the PRN group were included. There was no difference in demographics or baseline envenomation severity or hemotoxicity (32.7% vs 40.5%; respectively; $p = 0.158$) between the two groups. Comparing the PRN with the maintenance group, less antivenom was used (8 [interquartile range, 6–12] vs 16 [interquartile range, 12–18] vials, respectively; $p < 0.001$), and hospital length of stay was shorter (27 hr [interquartile range, 20–44 hr] vs 34 hr [interquartile range, 24–43 hr], respectively; $p = 0.014$). There were no differences in follow-up outcomes of readmission, retreatment, or bleeding and surgical complications.

Conclusions: Hospital length of stay was shorter, and less antivenom was used in patients receiving a PRN antivenom dosing strategy after rattlesnake envenomation. (*Crit Care Med* 2018; XX:00–00)

Key Words: antivenom; coagulopathy; envenomation; rattlesnake; thrombocytopenia

Each year, approximately 10,000 patients are treated for snakebites in the United States (1). Although mortality after native envenomations is low (2), morbidity is significant, inclusive of local tissue injury, hematologic toxicity, and more rarely necrosis, bleeding, compartment syndrome, and shock (3, 4). The mainstay management of snakebites and associated complications is antivenom; however, this antidote can pose a substantial financial burden to hospitals and patients. A single vial of wholesale antivenom costs approximately $2,300, and patients can be charged significantly more. An average of 10 vials or more are often required to manage a single snakebite injury (5). Additional antivenom may be required in a delayed fashion, as it is not uncommon for patients to develop recurrence or late onset of hematologic disturbances (collectively labeled late hemotoxicity) after initial hospital discharge (6).

Manufacturer instructions for Crofab (BTG International, West Conshohocken, PA) recommend maintenance dosing of antivenom, consisting of two vials given 6, 12, and 18 hours after establishing initial control of the envenomation. The use of maintenance adds a mandatory six additional vials of antivenom after control is established. A primary rationale behind routine maintenance dosing of antivenom is that additional staggered doses may reduce the occurrence of both early and late recurrences. The evidence to support this theory remains insufficient. With regard to late recurrence, the data to support maintenance dosing are limited to an initial series of 30 patients (7).

Concern over the high cost of antivenom without clear benefit of maintenance dosing has led some toxicologists to dose antivenom on an as-needed (PRN) basis after control

[1]Department of Emergency Medicine, Division of Medical Toxicology, University of Southern California, Los Angeles, CA.

[2]Department of Critical Care Medicine, University of Pittsburgh Medical Center, Presbyterian/Montefiore and Mercy Hospitals, Pittsburgh, PA.

[3]Department of Medical Toxicology, Banner–University Medical Center Phoenix, Phoenix, AZ.

[4]Division of Medical Toxicology and Precision Medicine, Department of Emergency Medicine, University of Arizona College of Medicine, Phoenix, AZ.

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For information regarding this article, E-mail: mspyres@gmail.com

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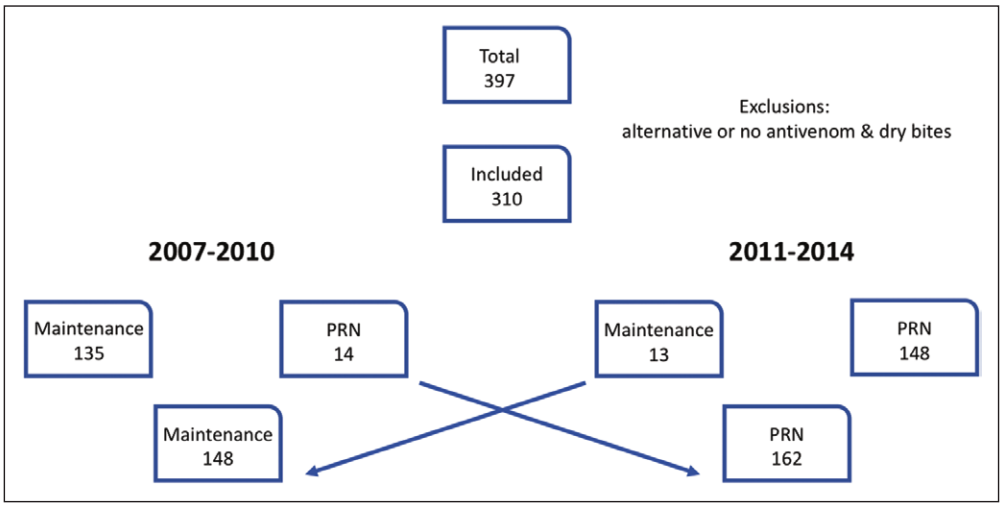

Figure 1. Maintenance and PRN groups. Breakdown of allocation to maintenance and PRN groups.

is established. Notably, however, PRN dosing of antivenom requires frequent bedside reassessment by a physician trained in the management of envenomated patients, typically a medical toxicologist. In the PRN strategy, the patient is observed over the 18-hour period in which maintenance dosing is typically given and administered additional antivenom for progression of local tissue effects, persistent or worsening of hemotoxicity, or systemic signs of envenomation. The PRN dosing strategy does not provide a strict algorithm for timing of antivenom redosing or for the number of vials administered but rather relies on expert physician evaluation and reassessment. Comparative outcomes of these two practices, including hematologic sequelae, antivenom utilization, hospital length of stay, and recurrence, are not well described. This study aims to better characterize differences in the above outcomes between the two dosing strategies, with the hypotheses that there is no difference in length of hospital stay or number of vials of antivenin used between the two treatment strategies.

METHODS

Study Design

This is a retrospective cohort study of adult rattlesnake envenomations treated at a regional toxicology center comparing maintenance and PRN antivenom dosing strategies. The primary outcomes of this study were hospital length of stay and total vials antivenom used, compared between the two dosing strategies. Secondary outcomes, including readmission, retreatment, bleeding, surgery, and hemotoxicity were analyzed in an exploratory manner. This study was approved by the Institutional Review Board at the study institution, and a waiver of informed consent was obtained.

Setting

Patients admitted to a regional toxicology service for rattlesnake envenomation between 2007 and 2014 were included. The toxicology service is part of a single-center 658-bed hospital in Phoenix, AZ.

Patients

Patients were included if they were greater than or equal to 14 years old and excluded if they did not receive antivenom for any reason inclusive of dry bites (struck by snake but no venom delivered) or if they received any antivenom other than Crofab (**Fig. 1**).

Data Collection

Data collected included demographics, details of envenomation and treatment, laboratory data, and initial and follow-up clinical outcomes. Data collection was completed by study authors (M.B.S., A.B.S., E.C.M., A.P.J, A.M.R.) after a training period. A random selection of charts was reviewed by an author (M.B.S) for errors or inconsistencies, and no significant issues were detected.

Prior to 2011, maintenance dosing of antivenom was standard practice at the regional toxicology center. The regional toxicology center had routinely acted as the admitting service for rattlesnake envenomations for 30 years at the time of this study. In 2011, the practice policy at the study institution changed from routine use of maintenance dosing antivenom to a clinical- and laboratory-triggered (PRN) dosing strategy. Patients were divided into two groups for analysis. The first group included patients treated with maintenance dosing, and the second group included patients treated with PRN dosing. The study period was defined as 2007–2014 to provide an equal time period for each dosing strategy.

Maintenance dosing was defined as two vials of antivenom administered every 6 hours × three doses after the initial bolus doses of antivenom were given to control, or stop progression, of the envenomation. Patients receiving rescue doses for loss of control were included in this group provided maintenance dosing was also administered. PRN dosing was defined as the absence of maintenance dosing. Hemotoxicity was defined as the presence of thrombocytopenia (platelets < 120 K/mm^3) or coagulopathy (fibrinogen < 170 mg/dL) occurring at any point during the initial hospitalization. Surgical procedures were defined as any surgical intervention beyond simple wound debridement. Patients were identified based on *International Classification of Diseases,* 9th Edition, codes (989.5, E905.0, and E906.2) for envenomations and by review of the center's internal log book of cases.

Statistical Analysis

Descriptive statistics were used with continuous variables reported as medians and interquartile range (IQR) and categorical variables as percentages. chi-square analysis was performed for categorical data, and independent *t* tests and Mann-Whitney *U* tests were performed for continuous data. Patients were analyzed based on the dosing strategy administered, regardless

of the practice policy at the time of treatment. A sensitivity analysis was performed by not excluding those patients who were not treated with the strategy appropriate for the time period.

Sample Size

Power calculations were performed a priori. Regarding continuous variables, to detect a 50% increase in ICU or hospital length of stay with 80% power and alpha 0.05, and mean estimated length of stay 48 hours (range, 24–72 hr), we required a minimum sample size of 32 patients per group. In order to detect a 10% increase in number of vials of antivenom administered with 80% power and alpha 0.05, and mean estimated number of vials 12 (range, 10–14 vials), we required a minimum sample size of 126 patients per group.

RESULTS

Cases

Between January 1, 2007, and December 31, 2014, 397 rattlesnake envenomations in adults were identified and 310 met inclusion criteria. Rattlesnake species were not reliably identified. One-hundred forty-nine envenomations occurred from 2007 to 2010 during the maintenance period, and 161 envenomations occurred from 2011 to 2014 during the PRN period. One-hundred thirty-five envenomations were treated with maintenance dosing in the maintenance period, and 148 were treated with PRN dosing in the PRN period. There were 14 patients treated with a PRN dosing schedule in the maintenance period, and 13 patients treated with maintenance dosing schedule in the PRN period (Fig. 1).

Presentation and Initial Hospitalization

Baseline patient characteristics, including age, sex, location of bite, the presence of systemic symptoms of envenomation, and prior envenomation history, were similar (**Table 1**). Initial laboratory values on arrival to the emergency department were also similar between groups. In the PRN compared with the maintenance group, median initial hemoglobin (g/dL) was 15.1 (IQR, 14.1–16.0) and 15.3 (IQR, 14.1–16.2), *p* value equals to 0.617; median initial prothrombin time (s) was 12.8 (IQR, 11.6–13.8) and 13.1 (IQR, 11.4–14.1), *p* value equals to 0.197; median initial fibrinogen (mg/dL) was 304 (IQR, 247–363), and 270 (IQR, 234–341), *p* value equals to 0.086; median initial platelets (K/mm^3) was 212 (IQR, 158–248) and 200 (IQR, 145–256), *p* value equals to 0.276, respectively. Median initial antivenom dose was six vials for both the PRN (IQR, 4–6 vials) and maintenance (IQR, 6–6 vials) groups.

Time to antivenom was 2.7 hours (IQR 1.8–4.3 hr) in the PRN group and 3.0 hours (IQR, 2.2–5.3 hr) in the maintenance group ($p = 0.04$).

During the initial hospitalization, there was no difference in median hematologic outcomes between the two groups (**Table 2**). Hemotoxicity occurred in 53 unique cases (32.7%) in the PRN group and 60 unique cases (40.5%) in the maintenance group ($p = 0.158$). There was no difference in occurrence of thrombocytopenia or coagulopathy between the two groups in the initial hospitalization (**Table 3**).

Total median vials antivenom used was 8 (IQR, 6–12) in the PRN group and 16 (IQR, 12–18) in the maintenance group ($p < 0.001$). ICU length of stay was 20 hours (IQR, 16–29 hr) in the PRN group and 25 hours (IQR, 20–37 hr) in the maintenance group ($p < 0.001$). Total length of stay was 27 hours (IQR, 20–44 hr) in the PRN group and 34 hours (IQR, 24–43 hr) in the maintenance group ($p = 0.014$).

The data were analyzed separately to exclude cross-over cases. For PRN versus maintenance excluding cross overs, total vials antivenom used was 8 and 16 ($p < 0.001$), ICU length of stay was 20 versus 24 hours ($p < 0.001$), and total length of stay was 28 versus 33 hours ($p = 0.038$), respectively.

Follow-Up

Follow-up data were available for 287 patients (92.6%), with 155 (95.7%) in the PRN group and 132 (89.2%) in the maintenance group. There was no difference in rates of readmission, retreatment, bleeding, or surgical procedures on follow-up (**Table 4**).

TABLE 1. Patient and Envenomation Characteristics

Characteristics	PRN ($n = 162$) (%)	Maintenance ($n = 148$) (%)	*p*
Age, *n*	48	45	0.137
Men	79	76	0.483
Upper extremity bite	59	58	0.857
Vomiting	6.8	9.6	0.408
Diarrhea	3.1	1.4	0.452
Bleeding	3.7	2.7	0.753
Shock	4.3	6.2	0.609
Angioedema	1.2	1.4	1.000
Prior envenomation	8.6	6.8	0.546
Prior antivenom	4.9	1.4	0.108

DISCUSSION

This is the largest study to date comparing PRN and maintenance antivenom dosing strategies for rattlesnake envenomation. A key finding in this study is improved patient-centered outcomes, including shorter hospital length of stay and less antivenom administered in patients receiving the PRN dosing strategy. These patient-centered favorable outcomes were achieved without negative consequences on venom-associated hemotoxicity during the initial hospitalization. Follow-up laboratory values were not reported, preventing a true comparison of late hemotoxicity between the two strategies. Despite the lack of follow up laboratories, there was no difference in readmissions, retreatment, or complications on follow-up. Such findings strongly indicate no difference in clinically significant

TABLE 2. Median, Maximum, and Nadir Hematologic Variables

Laboratory Values	PRN ($n = 162$)	Maintenance ($n = 148$)	p
Hemoglobin nadir g/dL, median (IQR)	13.4 (12.4–14.5)	13.5 (12.2–14.5)	0.902
Prothrombin time maximum, s, median (IQR)	14.7 (13.9–16.0)	14.7 (13.0–17.1)	0.553
Fibrinogen nadir mg/dL, median (IQR)	234 (173–284)	227 (158–273)	0.365
Platelet nadir K/mm^3, median (IQR)	178 (132–217)	171 (115–211)	0.173

IQR = interquartile range.

TABLE 3. Hemotoxicity

Laboratory Values	PRN (% Total PRN)	Maintenance (% Total Maintenance)	p
Thrombocytopenia (platelets < 120 K/mm^3)	31 (19.1)	40 (27.0)	0.106
Coagulopathy (fibrinogen < 170 mg/dL)	31 (19.1)	39 (26.4)	0.137
Unique cases of hemotoxicity	53 (32.7)	60 (40.5)	0.158

TABLE 4. 60-Day Outcomes

Outcomes	PRN (% Total)	Maintenance (% Total)	p
Readmission	12 (7.7)	12 (9.1)	0.831
Retreatment	6 (3.9)	7 (5.3)	0.583
Bleeding	1 (0.6)	3 (2.3)	0.337
Surgery	4 (2.6)	5 (3.8)	0.737

late onset or recurrent hemotoxicity between the two groups, a patient-centered outcome more remarkable than laboratory markers. This finding is particularly significant as it contradicts a rationale often cited for the use of maintenance dosing, namely the prevention of recurrent hemotoxicity.

The retrospective study design has potential to add bias to the results. The fact that the practice policy at the institution was clearly defined as one strategy and then later the alternative, helps to eliminate some potential bias. However, physicians were free to choose his or her preferred dosing strategy for each case, resulting a total of 27 cross-over cases that received a dosing strategy inconsistent with the practice policy at that time. It is reasonable to presume that there may have been something inherently different in these cross-over cases, potentially introducing bias. For example, during the PRN dosing years, the treating physician may have chosen to use maintenance dosing for a more severe envenomation. Alternatively, the decision to use maintenance dosing may have simply been the physician preference for that strategy applied evenly to all cases. The retrospective design of this study prevents further clarification of this issue. To address this problem, a separate analysis excluding the cross-over cases was performed, and no difference in outcomes was found. This persistent finding of favorable outcomes for the PRN strategy strengthens the results of this study. We did not reanalyze the data in an "intent to treat" manner, as this was not a randomized controlled trial with randomization. We were not concerned with affecting the "equality" of the groups by analyzing patients based on the treatment received.

Of note is the shorter time to antivenom in the PRN when compared with the maintenance group (2.7 vs 3.0 hr, respectively). Although no data exist to confirm this, it is reasonable to presume that delay in administration of antivenom would lead to worse outcomes, and conversely that earlier treatment would be associated with better outcomes. Although the time difference between the two groups was statistically significant, the clinical significance of 12-minute delay in antivenom administration is certainly questionable. It is the authors' opinion that this difference in time to antivenom administration was unlikely to play a significant role in outcomes.

A previous study found similar results with regard to reduced length of stay for envenomated patients treated by medical toxicologists (8). Shorter ICU and hospital length of stay and less total antivenom used has the potential for significant impact on reduction of costs both to the hospital and to the patient. Using a wholesale cost of antivenom of $2,300 per vial, a reduction from 16 to eight vials as shown in this study would save $18,400 per case in antivenom costs (9, 10). Considering the large in-hospital mark-up in charges for antivenom therapies, the actual cost savings to the patient would be much more significant (9). Hospitals would benefit directly from additional savings gained from shorter ICU and hospital lengths of stay. It should be noted that although use of additional antivenom may be linked to increased length of stay, it remains true that both variables will increase hospital costs.

Importantly, as medical toxicologists continue to push to establish our worth as integral parts of a hospital system, financial savings are an essential piece of that argument. Although this study did not directly compare medical toxicologists with other physicians, the practice of safely modeling this study and converting to a PRN antivenom dosing strategy reasonably requires a physician expert in envenomations, most typically a medical toxicologist. In this model, costs savings will result

both from expert utilization of an expensive antidote and from shortened hospital length of stay, all while maintaining positive patient-centered clinical outcomes.

This study is limited by its retrospective design. Although the practice policy guidelines reduced possible bias of physician-selected treatment, patients were not formally randomized to each dosing strategy. Additionally, the maintenance dosing strategy occurred during a 4-year period that preceded the PRN strategy. Although this time discrepancy allowed for potential advancements in care to favor the later PRN years, very few changes in snakebite management occurred during that period. Additionally, the treating faculty physicians largely remained consistent over the 8 years of the study, both of which would limit the potential effect of the time discrepancy.

An important limitation of this study is its occurrence at a single center. This center is unique among other toxicology practices in that it maintains its own admitting service staffed 24/7 by medical toxicology fellows and full-time toxicology faculty practicing at the bedside. It is difficult to extrapolate findings from this center to other practices that do not routinely engage in bedside management of patients by medical toxicologists. Additionally, rattlesnakes make up the majority of envenomations treated at the study center, limiting extrapolation of study findings beyond rattlesnake envenomations.

Data abstractors were not blinded to the study hypothesis which could introduce bias. Data abstracted from charts were limited to objective data, and the findings in this study were contradictory to the hypothesis, mitigating this limitation.

Children were not included in this study, and the results cannot be extrapolated to apply to this population.

CONCLUSIONS

In this study, hospital and ICU lengths of stay were shorter, and less antivenom was used in patients receiving a PRN dosing strategy for antivenom after rattlesnake envenomation. These improvements were achieved without negative consequences in follow-up outcomes, including readmission, retreatment, as well as bleeding and surgical complications.

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