

Article type : Original Contribution

**ASSESSING THE EFFECT OF A MEDICAL TOXICOLOGIST IN THE CARE OF RATTLESNAKE ENVENOMATED PATIENTS.**

Michael Levine MD<sup>1</sup>, Steve Offerman MD<sup>2</sup>, Rais Vohra MD<sup>3</sup>, Brian Wolk MD<sup>4</sup>, Jeff Lapoint DO<sup>5</sup>, Dan Quan DO<sup>6</sup>, Meghan Spyres MD<sup>1</sup>, Frank LoVecchio DO<sup>7</sup>, Stephen H. Thomas MD, MPH<sup>8</sup>

1. Department of Emergency Medicine, Division of Medical Toxicology. University of Southern California, Los Angeles CA
2. Department of Emergency Medicine, division of Medical Toxicology. Kaiser South Sacramento. Sacramento, CA
3. Department of Emergency Medicine, UCSF Fresno Medical Center. Fresno, CA
4. Department of Emergency Medicine. Loma Linda Medical Center. Loma Linda, CA
5. Department of Emergency Medicine. Kaiser San Diego. San Diego, CA
6. Scottsdale Healthcare. Scottsdale, AZ
7. Department of Emergency Medicine, Maricopa Medical Center. Phoenix, AZ
8. Weill Cornell College of Medicine in Qatar and Hamad Medical Corporation, Department of Emergency Medicine, Doha, Qatar

Disclosures: There are no financial, litigational, or other conflicts of interest to disclose

Author contribution:

Dr. Levine conceived the study, performed data abstraction, assisted with manuscript preparation, and takes responsibility for the study in its entirety.

Drs. Offerman, Vohra, Wolk, Lapoint, and Quann assisted with data abstraction and manuscript preparation

Drs. Spyres and LoVecchio assisted with study design, data abstraction, and manuscript preparation

Dr. Thomas assisted with study design and manuscript preparation. Dr. Thomas performed all of the statistical analysis.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/acem.13401

This article is protected by copyright. All rights reserved.

## **ASSESSING THE IMPACT OF A MEDICAL TOXICOLOGIST IN THE CARE OF RATTLESNAKE ENVENOMATED PATIENTS.**

Corresponding author mail id:mdlevine@usc.edu

### **ABSTRACT**

Rattlesnake envenomation is an important problem in the United States, and the management of these envenomations can be complex. Despite these complexities, however, the majority of such cases are managed without the involvement of a medical toxicologist. The primary objective of this study is to evaluate the impact of a medical toxicology service on the length of stay of such patients. Methods: The authors conducted a retrospective study at six centers in California and Arizona. Patients were included if they were admitted in the two years before the establishment of a medical toxicology service (pre-MTS) or in the two years after the creation of a medical toxicology service (post-MTS). Results: A total of 300 subjects were included (169 pre-MTS; 131 post MTS). Baseline characteristics between the pre-MTS and post-MTS group were very similar. The creation of a medical toxicology service was associated with a significant reduction in the length of stay (69.5 [59.1-79.9] vs. 48.1 [41.4-54.8] hours). This reduced length of stay was not associated with any statistically significant change in readmission rates. Conclusion: Rattlesnake bite patients treated by a medical toxicologist have a significant reduced length of stay compared to those without direct involvement of a medical toxicologist.

### **INTRODUCTION**

Rattlesnake envenomation remains an important health problem, with nearly 9,000 patients treated for snakebite annually in the United States.<sup>1</sup> Although mortality is low, rattlesnake envenomations are associated with significant morbidity and cost. The management of such envenomations ideally involves intensive evaluation and reassessment. In addition, specific post discharge instructions and

Accepted Article

re-evaluations are recommended.<sup>1</sup> In 2015, poison information specialists at US poison control centers assisted healthcare facilities in the management of more than 3500 snakebites.<sup>2</sup> Medical toxicologists, physicians with specialized training in envenomations, frequently provide guidance to the poison information specialists remotely managing these patients. Additionally, when available as a consulting or admitting service, medical toxicologist provide direct care at the bedside of envenomated patients. The involvement of a toxicologist in the care of poisoned patients in general is associated with reduced length of stay (LOS), and possibly reduced healthcare costs.<sup>3-6</sup> It is unclear, however, what role a medical toxicology service (MTS), in which a medical toxicologist is providing direct patient care, provides in patients with rattlesnake envenomations. The primary objective of this study is to evaluate the impact of a MTS on the LOS of patients with rattlesnake envenomations.

## **METHODS**

This study is a retrospective study of patients evaluated at six different medical centers in California following rattlesnake envenomation. These centers include two university-affiliated teaching hospitals, two community teaching hospitals, one university-affiliated non-teaching hospital and one community non-teaching hospital. Each of these centers established a medical toxicology service between 2011-2015. At each of these centers, the toxicologist serves as a consultant, and has formal consulting privileges. In all but one of the centers, the toxicologist did write orders for antivenom as a consultant and managed the issues related to the envenomation. Consults were provided by five independent toxicology groups at the six hospitals. Eligible patients were included if they presented after a known or suspected rattlesnake envenomation in the two years before (pre-MTS) or after (post-MTS) a toxicology service was created. . Patients were identified via search of ICD-9 (E905.0) codes. Bites due to known non-venomous snakes (e.g. pet king snake) were excluded. Definitive confirmation of the snake was not required. In addition, if, upon reviewing the

Accepted Article

record, the bite was clearly not due to a snake, but simply coded based on ICD-9 code, the record was excluded. This study was performed as an intent to treat analysis, such that each patient in the post MTS period, was included, even if toxicology was not consulted. The study was approved by the institutional review board at each of the participating medical centers.

### *Study definitions*

LOS was calculated in hours from presentation to the emergency department until discharge from the hospital. Maintenance therapy was defined as a scheduled order for three doses of antivenom, each six hours apart. Bleeding was defined as any bleeding beyond local oozing from the bite site. Poison control was considered to be involved if discussion with poison control was documented at any point during the patient's hospital stay.

### *Data abstraction*

Data were collected on a pre-designed data abstraction sheet by one member of the study team at each institution. Each reviewer received a brief training on data abstraction to ensure the abstraction was uniform at each site. The investigators were blinded to the study hypothesis. After data collection, data were entered into an Excel Spreadsheet (Microsoft, Redmond, WA). Baseline data abstracted from the medical record included age, sex, year of admission, study time period (pre or post initiation of MTS), location of the bite, past medical history, and use of antiplatelet or anticoagulant medications. The patient's LOS, initial, nadir, and final laboratory studies (prothrombin time, platelets, and fibrinogen), incidence of bleeding, and involvement of a poison control center were recorded. Treatment with antivenom, non-steroidal anti-inflammatory drugs, antibiotics, blood products, and incidence of surgical intervention was abstracted. Lastly, length of

stay, administration of rattlesnake-specific discharge instructions, and readmission for complications related to the snakebite were recorded.

#### *Outcome measures*

The primary outcome in this study was hospital LOS. Additional outcomes evaluated included total vials antivenom used, maximum and nadir laboratory values, administration of blood products, antibiotics, and non-steroidal anti-inflammatory drugs, incidence of surgical intervention, and bleeding and readmission for snakebite related complications.

#### *Data analysis*

The data from these six medical centers was pooled and analyzed in a before/after model.

Continuous data, all of which were found to be non-normal by Shapiro-Wilk testing, were analyzed for central tendency using median and interquartile range (IQR). Proportions were reported with 95% confidence intervals (CIs) which were calculated using binomial exact methods.

Univariate analysis was utilized to assess whether there were apparent changes in patient complexity or acuity between the study period's pre-MTS and MTS groups, in order to inform decisions as to whether any differences were identified that prompted a need for multivariate regression modeling. Kruskal-Wallis nonparametric methods were utilized for initial analysis of continuous variables, and chi-square analysis and Fisher's exact testing (when any cell value fell below five) were used for categorical variables.

When significant differences were identified in univariate testing, standard epidemiological measures were calculated. The measures of relative risk were the risk ratio and risk difference (with the inverse of the latter used to calculate number needed to treat).

An *a priori* decision was made to analyze the primary endpoint (LOS) with non-parametric Kruskal-Wallis testing first. Then, only if the non-parametric  $p$  was significant, with parametric techniques (the  $t$  test) to accurately estimate the effect magnitude. This approach is conservative, as it avoids use of techniques such as bootstrapping (for 95% CIs for medians) and if anything would underestimate the significance of any MTS effect on LOS.<sup>7-9</sup>

In order to assess the median differences in the pre- and post-MTS periods for each of the MTS services, two approaches were taken. First, the LOS for the pre- and post-MTS periods were tabulated for each of the 5 MTS groups (5 services covered 6 hospitals). Next, the overall group of pre- and post-MTS periods' LOS data were tabulated. The overall pre- vs. post-MTS period LOS results were compared using Wilcoxon rank-sum testing, to assess the null hypothesis of zero difference between the medians of the two groups. In order to provide conservative calculations, Stata's *cen dif* procedure was used, in order to provide a robust calculation of the (Hodges-Lehmann) median difference (with 95% CI) between the pre- and post-MTS periods, clustered on MTS group

Variables assessed to determine whether patient characteristics were similar between the pre-MTS and MTS groups included patient demographics and medical history, information regarding diabetes status, anticoagulation therapy, and known liver disease. Additional information used to assess

Accepted Article

patient acuity at index-visit ED presentation included the initial coagulation laboratory parameters, number of antivenom vials in first treatment, and bite location (categorized as to hand, foot, non-hand or non-foot extremity, or other location).

## RESULTS

A total of 302 patients were identified. Upon review of the records, two patients were bitten or stung by non crotalidae and thus were excluded. Thus, the final population included 300 patients. There were 169 patients in the pre-MTS cohort, and 131 patients in the post-MTS cohort. A toxicologist was involved in 0 of the cases in the pre MTS cohort, whereas a toxicologist was involved in 99 (76%) cases in the post MTS group. Overall, males accounted for 228 (76%) of all subjects. The majority of the bites were to the hand (60.3%), foot (20%), and non-foot lower extremity (15.3%). The median (interquartile range) age was 44 (22-55.5) years.

There were no significant differences observed in the baseline parameters between the two groups. Shock on presentation was uncommon (2.4% vs 2.3% in the pre-MTS and post-MTS groups, respectively). Similarly, there was no difference in initial hematologic parameters between the two groups. See table I. Based upon these negative findings in univariate analysis, in accordance with *a priori* methods planning, there was no requirement to proceed with multivariate analysis in order to assess a possible association between MTS status and LOS.

LOS was significantly shorter for post-MTS as compared to pre-MTS cases (48.1 [41.4-54.8] hours vs. 69.5 [59.1-79.9] hours;  $p=0.014$ ) in non-parametric analysis. The reduction in LOS associated with the post-MTS compared to the pre-MTS group was 21.4 hours (95% CI 8.2-34.5 hours). Overall,

documented poison control assistance was low in both the pre-MTS and post-MTS groups ( 13% vs. 10.8%, respectively;  $p=0.554$ ). There was no difference in the total vials antivenom administered (10 (6-16) vials pre-MTS and 12 (6-20) vials post-MTS;  $p=0.09$ ) However, the use of maintenance dosing of antivenom was somewhat higher in the post MTS group compared with the pre-MTS group, albeit still low in both group (31.5% vs. 17.8%; 95% CI 3.42-24%)

Antibiotics, however, were administered more often in the pre MTS group (18.3% vs. 10.0%;  $p=0.04$ ; risk ratio 1.8; 95% CI 1.0-3.4). There were no fatalities in either group.

Twenty-one patients (12.4%) of the pre-MTS group were re-admitted compared with 18 (13.9%) in the post MTS group ( $p=0.718$ ). See table II for complete outcome results.

## **DISCUSSION**

This study demonstrated the development of a MTS was associated with decreased length of stay, with similar rates of antivenom administration and readmission rates.

While the study was retrospective, the available data suggest little, if any clinically important difference in baseline characteristics between the two groups. None of the demographic, laboratory, or medical parameters assessed between the two groups with respect to initial presentation differed significantly. While the apparent similarity of the two groups with respect to all assessed parameters does not eliminate the possibility of residual confounding, we find no evidence of such. Furthermore, the magnitude of the LOS reduction associated with a MTS presence is such that it seems unlikely explainable by unmeasured variables. The implementation of the MTS

Accepted Article

occurred at different years in different hospitals. Thus, it is unlikely that the decreased LOS was the result of a national change in practice management.

Antibiotics are not routinely indicated for crotaline bites in North America.<sup>10</sup> Implementation of a MTS was associated with a reduction in antibiotic therapy (18% vs. 10%)

The most important finding was that the *a priori* primary endpoint, LOS, was shorter for the MTS cases than the pre-MTS cases. The difference was clinically, administratively, and statistically significant. The MTS group status on univariate analysis was associated with nearly a full day's shorter LOS (over 21 hours). Such LOS reductions along these lines could be investigated as a major contributor to the cost-effectiveness of instituting MTS in hospitals such as the study centers. Importantly, the reduction in length of stay associated with a MTS was associated with similar readmission rates. While it is possible that readmissions would be missed if the patient presented to a hospital outside of the study site, it is unlikely this would be significantly different in the pre vs post MTS. However, one could imagine a case that the readmission rate would be higher in the post MTS group, as the toxicologists were following the patients as out patients, whereas a hospitalist would typically not follow the patient as an outpatient. In this study, several patients in the post MTS group were admitted to a hospitalist and the toxicologist was not consulted. Thus, if consults were obtained on each patient in the post MTS group, the results would likely be further magnified.

Given there is a reduction in the length of stay and a reduction in unnecessary treatments (e.g. antibiotics) while not increasing re-admission rates, an argument can be made that the involvement of a medical toxicologist in the care of a rattlesnake bite patient is associated with improved quality of care.

This article is protected by copyright. All rights reserved.

The exact cost savings are difficult to determine, and dependent on multiple variables, including the number of toxicologists, the volume of patients, etc. However, in one study, care of a poisoned patient by a toxicologist was associated with a cost savings of more than \$1000 per patient.<sup>3</sup> It is assumed, but not known definitively, that the involvement of a toxicologist in a rattlesnake bite patient would be associated with a significant cost savings. While there was a statistically significant decrease in the length of stay for patients in the MTS group, the study was not designed or intended to perform a cost analysis of a MTS or the overall costs associated with rattlesnake envenomated patients. As increased healthcare pressures exert more influence over hospitalizations and observation, such a prospective study may be of value.,

The use of maintenance therapy was greater in the post MTS group, but still remained relatively uncommon (18% vs. 32%). While one would expect increased use of maintenance antivenom to be associated with an increased LOS, it was not. Perhaps, this apparent discrepancy was because the increased level of expertise in the post MTS period lead to greater use in patients who needed it the most.

This study is similar to previous studies that have demonstrated potential benefit to a MTS. Curry and colleagues performed a severity-weighted comparison of the cost, length of stay, and percent mortality for their admitting service in comparison to the Premier database. The authors found their toxicology admitting service was associated with decreased length of stay and decreased morbidity with the added benefit of cost savings.<sup>3</sup> Vhora and colleagues established a medical toxicology service at their university-affiliated teaching hospital, and examined the length of stay in patients admitted with acetaminophen toxicity before and after the service was created.<sup>5</sup> The authors found

Accepted Article

a significant decreased length of stay after a medical toxicology service was created. Lastly, Lee and colleagues examined the length of stay in the 12 month period before and after a toxicology service was created at a major metropolitan teaching hospital in Australia. The authors found creation of the toxicology service resulted in increased number of patients treated while reducing the length of stay.<sup>6</sup> While other studies have examined the effect of a toxicologist in the care of an overdose patient, this is the first to examine the effect of a MTS on envenomated patients. Because of variability in administration of antivenom, it was not known, prior to this study, if a toxicologist's involvement in an envenomated patient would be associated with a reduction in the length of stay or the readmission rate compared to patients treated without the direct involvement of a toxicologist.

#### **LIMITATIONS**

This study is limited by its retrospective nature and consequently, any conclusions are limited by the quality and completeness of the data in the medical record. However, because the study primarily used continuous variables (e.g. number of hours in a hospital; fibrinogen, etc.) and dichotomous variables (e.g. documented surgical procedure or not), we feel these choices in the data abstracted likely reduced, if not eliminated abstractor bias, thereby minimizing some of the limitations inherent in a retrospective review.<sup>11</sup>

We did not control for poison control center involvement. While this is a potential limitation, given the relatively low involvement in both groups (36 total cases which were evenly distributed between the pre- and post-MTS groups), we do not feel this has a significant impact on our conclusions.

There were several patients in the post period that were not seen by a toxicologist. An *a priori* decision was made to analyze these patients based on pre MTS and post MTS, rather than involvement or no involvement of a toxicologist. It is impossible to know the benefit is the actual recommendations and presence at the bedside of the toxicologist, or just the fact that there is a service and intangible benefits associated with the MTS (e.g. teaching or “curb-side” consultations)..

## **CONCLUSION**

The implementation of a medical toxicology service was associated with a reduction in length of stay, without a corresponding increase in the amount of antivenom administered or re-admission

## **REFERENCES:**

1. Lavonas EJ, Ruha AM, Banner W, et. al. Unified treatment algorithm for the management of crocotaline snakebite in the United States: results of an evidence-informed consensus workshop. BMC Emergency Medicine. 2011; 11:2
2. Mowry JB, Spyker DA, Brooks DE, et. al. 2015 Annual report of the American Association of Poison Control Centers' national Poison Data System (NPDS): 33<sup>rd</sup> Annual report. Clin Toxicol. 2016; 54:924-1109
3. Curry SC, Brooks DE, Skolnik AB, et. al. Effect of a medical toxicology admitting service on length of stay, cost, and mortality among inpatients discharged with poisoning-related diagnoses. J Med Toxicol. 2015; 11:65-72.

- Accepted Article
4. Isoardi KZ, Armitage MC, Harris K, et. al. Establishing a dedicated toxicology unit reduces length of stay of poisoned patients and saves hospital bed days. *Emerg Med Australas.* 2017; 7: Epub (DOI: 10.1111/1742-6723.12755)
  5. Chang J, Vohra R, Levine M. Acetaminophen poisoning: Effect of a toxicology consultation service on length of stay on a single academic medical center. *J Med Toxicol.* 2016; 12:9
  6. Lee V, Kerr JF, Braitberg G, et. al. Impact of a toxicology service on a metropolitan teaching hospital. *Emerg Med.* 2011; 13:37-42.
  7. Haukoos JS, Lewis RJ. Advanced statistics: bootstrapping confidence intervals for statistics with “difficult” distributions. *Acad Emerg Med.* 2005; 12:360-5.
  8. Qualls M, Pallin DJ, Shuur JD. Parametric versus nonparametric statistical tests: the length of stay example. *Acad Emerg Med.* 2010; 17:1113-21
  9. Vickers AJ. Parametric versus non-parametric statistics in the analysis of randomized trials with non-normally distributed data. *BMC Med Res Methodol.* 2005; 5:35.
  10. Norris RL, Bush SP, Cardwell MD. Bites by venomous reptiles in Canada, the United States, and Mexico. In *Auerbach’s Wilderness Medicine.* Auerbach P, Cushing T, Harris NS (Eds.). 7<sup>th</sup> Edition. Elsevier. Philadelphia. 2017; 729-60

11. Gilbert EH, Lowenstein SR, Koziol-McLain J, et. al. Chart reviews in emergency medicine research: What are the methods? *Ann Emerg Med.* 1996; 27:305-8.

TABLE I:

Parameter	Pre-MTS N = 169	Post-MTS N = 131	<i>p</i>
Age median (IQR)	43 (22-55)	47 (22-57)	.411
Male N (%)	131 (77.5% of 169)	97 (74.1% of 131)	.485
Bite location N (% of 300)			.499
Hand	105 (62.1% of 169)	76 (58.0% of 131)	
Upper extremity (not hand)	5 (3.0%)	6 (4.6%)	
Foot	33 (19.5%)	27 (20.6%)	
Lower extremity (not foot)	26 (15.4%)	20 (15.3%)	
Other	0 (0%)	2 (1.5%)	
History of diabetes N (%)	10 (5.9% of 169)	8 (6.2% of 130)*	.932
Pre-bite aspirin therapy	3 (1.8% of 169)	7 (5.4% of 130) *	.085
Poison Control Center call	22 (13.0% of 169)	14 (10.8% of 130) *	.554
Lab values (median, IQR)			
Initial prothrombin time	11.5 (10.7-12.6)	12.2 (10.6-13.4)	.282
Initial platelet count	204 (171-251)	200 (157-249)	.505
Initial fibrinogen level	274 (227-327)	274 (235-325)	.773
Diffuse bleeding or shock on presentation	4 (2.4% of 169)	3 (2.3% of 130) *	1.00
Initial vials of therapy (median, IQR)	6 (4-6)	6 (4-6)	.831

\* Data were missing for one patient in the MTS group for this parameter. A denominator of 130 was used.

Table II: Therapy and outcomes in the pre-MTS and MTS groups.

Parameter	Pre-MTS N = 169	Post-MTS N = 131	p
Length of stay (mean, 95% CI for mean)	69.5 (59.1-79.9)	48.1 (41.4-54.8)	.002
Antivenom therapy; median (IQR)			
Total vials	10 (6-16)	12 (6-20)	.090
Use of maintenance-therapy regimen	30 (17.8% of 169)	41 (31.5% of 130)	.005
Laboratory parameters; median (IQR)			
Maximum prothrombin time	12 (11-13.4)	12.2 (11-14)	.881
Platelet count nadir	171 (137-211)	170 (139-206)	.749
Fibrinogen nadir	253 (209-296)	248 (217-287)	.976
Surgical intervention	1 (0.6%)	3 (2.3%)**	.321
Blood-product administration	5 (3.0%)	1 (0.8%)**	.238
Other medical therapy administered			
Intravenous antibiotics	31 (18.3%)	13 (10.0%)**	.044
Non-steroidal anti-inflammatory drugs	4 (2.4%)	0 (0%)**	.135
Instructions given for follow-up lab assessment	138 (81.7%)	116 (89.2%)**	.069
Readmission	21 (12.4%)	18 (13.9%)**	.718

\*\* Denominator of 130 patients, rather than 131 patients