2019 ACMT Annual Scientific Meeting
MedTox Shark Tank Research Forum

Primary Investigator: Kim Aldy, DO

Title: Bedside Ultrasound Evaluation and Indicators of Progression in Crotalid Snakebites

Aims:
his protocol is a pilot study on the use of POCUS for crotalid snakebites for the evaluation of extremity swelling and progression. In order to assess the sensitivity of ultrasound, we will first compare the reliability of an emergency physician (EP)/medical toxicologist (MT) in the use of POCUS for soft tissue swelling in cellulitis patients to an ultrasound-trained emergency medicine (EM) faculty. Our second aim seeks to compare two quantitative methods of assessment of local tissue swelling after crotalid envenomation between clinical and POCUS evaluation: (1) Measured depth at the site of maximal swelling within 2 cm of the envenomation site of the affected limb and the same site on the other limb using POCUS will be compared with circumferential measurements. The ratio between the affected limb and unaffected limb will be used to calculate the **expansion coefficient**. (2) Measured distance from the site of envenomation to the proximal leading-edge progression will be determined by the patient's own assessment, by visual/tactile exam, and by POCUS. This will be used to calculate the **percent expansion**, defined as the change in leading edge in one hour over the length of the extremity. Our third aim is to establish the interrater reliability for the measurement of soft tissue swelling of a crotalid envenomated limb by clinical visual/tactile evaluation and by POCUS evaluation. The evaluation will be performed in a similar manner as aim 2 with repeat measurements an hour later.

Specific Aim 1 (SA1): Compare the reliability of an emergency physician (EP)/medical toxicologist (MT) in the use of POCUS for soft tissue swelling in cellulitis patients to an ultrasound-trained emergency medicine (EM) faculty.

Specific Aim 2 (SA2): Compare the measurement of local tissue swelling from crotalid envenomation using clinical evaluation and POCUS evaluation.

- **2a:** Compare the POCUS **expansion coefficient** of a crotalid envenomated limb to circumferential limb measurement.
- **2b:** Compare the progression of proximal leading-edge by **percent expansion** of swelling through visual/tactile measurements to that of POCUS measurement.
- **2c:** Compare progression of proximal leading-edge by **percent expansion** of swelling using patients own determination versus both visual/tactile measurement and POCUS measurement.

Specific Aim 3 (SA3): Establish the interrater reliability for the measurement of soft tissue swelling of a crotalid envenomated limb by clinical visual/tactile evaluation and by POCUS evaluation.

- **3a:** Interrater reliability of limb circumference measurements as **expansion coefficient**.
- **3b:** Interrater reliability of measuring POCUS as **expansion coefficient**.
- **3c:** Interrater reliability of visual/tactile proximal leading-edge by **percent expansion**.
- **3d:** Interrater reliability of POCUS proximal leading-edge by **percent expansion**.

Significance and Innovation:

SA1: Sonographic features of SSTI are reliably visualized by EPs. Measurements of depth and approximation of the leading-edge in SSTI using POCUS have not been evaluated. In order to evaluate the sensitivity of ultrasound for snake envenomation, we will first need to demonstrate that quantifying the extent of soft tissue edema by an EP/MT reliably approximates that of an ultrasound-trained EP.

SA2: The evaluation of local swelling is highly subjective. Noting earlier progression using POCUS is important because this may lead to earlier treatment with antivenom which has been shown to improve limb functional recovery in copperhead envenomations.[9] After initial treatment decision, examination is required to decide if initial control is achieved or if re-bolus of antivenom is necessary. Given the cost and potential allergic reactions of antivenom, all decisions for administration of antivenom require the most reliable clinical and laboratory findings. Furthermore, one-quarter of snakebites by venomous snakes occur without any apparent venom injection.[10] If these so called “dry bites” are suspected, patients may be observed for at least 12 hours after being bitten, even if they are asymptomatic or have minimal local effects during their visit.[1] This can be a very difficult task for EPs in rural areas or at free standing EDs, where a lack of resources limits prolonged patient observation. Patients may be transferred to other hospitals via expensive and inherently risky ground/air transportation, tying up resources from other critically ill patients. Even in rural settings, the availability of POCUS is expanding.[11] Concurrently, POCUS training is a major focus of graduate medical education in multiple specialties, especially EM. Graduating EM residents are expected to be proficient in POCUS and are responsible for interpreting their own images.[3] Many EPs are regularly using POCUS for SSTI evaluation when physical exam is equivocal.[6] Additionally, POCUS use has been shown to decrease length of stay in pediatric SSTI cases.[12]

Our proposed aim would provide a basis for the sensitivity of ultrasound evaluation in snake bitten extremities. This work may lead to earlier noted progression of tissue destruction that can be halted, which may be associated with timely appropriate treatment, reduced patient pain and disability, and/or decreased hospital stay. The management of “dry bites” may undergo a paradigm shift, and patients may

be safety discharged after a much shorter ED length of stay without incurring the cost or risks of transfer to a tertiary care facility.
SA3: Management of the local effects after snakebite has been clinically and anecdotally treated. No data exists to describe the clinical evaluation of snakebites – either by visual/tactile evaluation or serial limb circumference measurements. Subaims 3a and 3c seek to objectively describe the reliability of clinical measurement techniques for snakebites. Similarly, very little is known about the utility of POCUS in relation to the evaluation of snakebites or the reliability of these assessments. Subaims 3b and 3d will provide a basis for the reproducibility of ultrasound evaluation in snake bitten extremities.

Research Methods and Timeline:
Study setting: This study will be conducted at three urban hospitals within the University of Texas Southwestern (UTSW) system in Dallas, Texas. Parkland Medical Center (PMH) is a county hospital with approximately 150,000 annual patient visits. Clements University Hospital (CUH) is a research and teaching hospital with 48,000 annual patient visits. Children's Medical Center (CMC) has about 90,000 patient visits annually. All of our hospitals are tertiary referral centers. Our MT fellows and faculty rotate call for the North Texas Poison Control Center and provide bedside toxicology consults at all three hospitals. Over the last 5 years, our MT bedside consult service has provided an average of 36 snakebite consults per year.

Study eligibility:
SA1: This study will be performed at PMH as a convenience sample of adult patients over the age of 18 years old with recently diagnosed extremity cellulitis requiring admission. Prisoners, pregnant patients, or amputees will be excluded. Informed consent will be obtained from the patient or next of kin.
SA2 and SA3: All Patients with a suspected crotalid envenomation are eligible.
Inclusion criteria:

- Suspected snakebite to an extremity with a reliable history PLUS clinical exam consistent with local effects of crotalid envenomation (erythema, swelling, pain, and/or ecchymosis).
- Determination of crotalid species by one of the following: clinician identification of snake specimen or photo, patient identification by photograph lineup, or patient bitten by captive snake.
- Bite occurred < 12 hours prior or being seen at the primary hospital.
- Bite occurred < 24 hours prior to toxicology consult being placed by primary clinical team.

Exclusion criteria: Prisoner, pregnant patient, amputee, or a patient who sustained snakebites to bilateral lower or bilateral upper extremities.

Study design:

SA1: Measurements will be performed at the visually determined site of maximal swelling and on the unaffected extremity at an identical anatomical location. POCUS will be used for depth measurements taken from skin to bone in the transverse plane using a high frequency linear probe (7–12 MHz). Tape measure will be used for circumferential measurements in similar locations. These measurements will be used to calculate an **expansion coefficient**, the ratio between the measured affected limb and unaffected limb. We will also take tape measurements of the area affected from the distal to proximal leading-edge as deemed by tactile/physical and POCUS. In addition, the affected extremity will be measured along the anterior anatomical plane from the middle finger to the AC joint in the upper extremity, or the big toe to the groin on the lower extremity. These measurements will be used to calculate **percent affected**, defined as the percent of the extremity that is affected by cellulitis.

SA2: *Patient identification and enrollment*: As part of our existing toxicology consult service, anytime a snakebite arrives to one of our affiliate hospitals, the primary team places a consult by paging our shared toxicology pager. A toxicology fellow and/or staff will typically evaluate envenomated patients within 1-2 hours because of the time sensitive nature of the injury and treatment. Those patients who meet all inclusion/exclusion criteria will be approached for study participation by a study personnel within 2 hours of our service being notified of the patient's arrival. For minors, consent will be obtained from a parent or legal guardian. If an adult patient is considered not capable of giving informed consent for participation due to distress or pain medication their next of kin will be approached for consent.

Measurement of the Limb Circumference Expansion Coefficient (LCEC): At a site visually determined to have maximum swelling within 2 cm of the suspected envenomation site, a tape measure will be used to measure the limb circumference. The location of the tape measure will be marked with a skin marker on both sides of the tape, and on the anterior and posterior limb to allow repeated future measurements. Measurement will be recorded to the nearest centimeter. The circumference will also be measured at an approximate location on the unaffected contralateral limb to mirror the measurement site of the envenomated limb. The **LCEC** is defined as the ratio of the circumference of affected limb to the circumference of the unaffected limb.

Measurement of the Sonographic Expansion Coefficient (SEC): At the same site as the circumference measurement, the depth of swelling will be measured from skin to bone in the transverse plane using a high frequency linear probe (7–12 MHz). If the maximal site of swelling is on the hand or foot, the water bath method will be used to improve visualization.[13] The sonographic measurement of the tissue planes will also be measured an approximate location on the contralateral limb to mirror the measurement site of the envenomated limb. The **SEC** is defined as the ratio of sonographic depth of swelling of the measured affected limb to the depth of swelling at the same location on the unaffected limb.

Self-Evaluation of Leading Edge (SE): Prior to any measurements or markings by staff or physicians, the patient (≥ 6 years) will use an arrow sticker to mark where he/she feels the most proximal leading edge of swelling to the limb is located. A trained research assistant (RA) will measure the distance from the envenomation site to the proximal leading edge to the nearest centimeter – denoted as variable **SE_1**. The RA will remove the sticker to blind the next evaluator of the previous measurement. The RA will also measure the patient's full affected extremity along the anterior anatomical plane from the middle finger to the AC joint in the upper extremity, or the big toe to the groin on the lower extremity – denoted as **limb length (LL)**. One hour after the initial measurement, regardless of treatment with or without antivenom, the patient will again mark the proximal leading edge for the RA. This second measurement will be denoted **SE_2**. The **percent expansion of self-evaluation (PE_{SE})** will be calculated as a percentage of the ratio of the difference between SE_1 and SE_2 over limb length.

Visual/Tactile Evaluation of Leading Edge (VTE): After the patient's self-evaluation, a study team provider will mark the leading edge of swelling by visual/tactile evaluation of the affected limb. The provider will mark the location for the RA to measure – denoted as **VTE_1**. One hour later, the same provider will mark the new leading edge as **VTE_2**. The **percent expansion of the visual/tactile evaluation (PE_{VTE})** will be calculated as a percentage of the ratio of the difference between VTE_1 and VTE_2 over limb length.

Sonographic Evaluation of Leading Edge (USE): After the patient's self-evaluation and the visual/tactile evaluation, a trained provider (part of the study team) will mark the leading edge of swelling as determined by a high frequency linear ultrasound probe (7–12 MHz) in the transverse plane. The ultrasound provider will mark the location for the RA to measure – denoted as **USE_1**. One hour later, the same provider will mark the new leading edge as **USE_2**. The **percent expansion of the sonographic evaluation (PE_{USE}),** defined as the percent of the bitten extremity that is affected by the envenomation, calculated as a percentage of the ratio of the difference between USE_1 and USE_2 over limb length.

SA3: The above measurements (LCEC, SEC, visual/tactile and sonographic evaluation of leading edge) will be performed by a toxicologist and another available physician on the primary team. A repeat measurement in the same manner will be performed by the same toxicologist and ED physician one hour later. If the same ED physician is not available at the time of repeat measurement, then another ED provider will be asked. All physical measurements will be rounded to the nearest centimeter. All evaluators will be blinded to the patient notes and prior clinical grading.

Data handling and study ethics:
In order to maintain confidentiality of patient protected health information (PHI), enrolled patients will be entered into a master list where only patient medical record number and corresponding hospital will be listed along with an assigned study identification number. This number will be entered in a separate excel datasheet where all non-PHI data will

be kept. These electronic files will be maintained on the UTSW SharePoint, a HIPAA compliant cloud storage that can only be accessed by UTSW employees and shared solely with our study group. All parts of the study will be submitted to the UTSW Institutional Review Board for review, who oversees research performed at our three hospitals. To ensure that treatment decisions are not being made based on the ultrasound findings, the study evaluation will not be performed by the toxicologist that is guiding treatment for the patient.

Statistical analysis:

SA1 – Sample size and precision for ICC: An ICC of 0.75 or more is expected between the EP/MT and ultrasound-trained EM evaluators. N=25 cellulitis patients will yield ICC precision of ± 0.19 (half-width of 95% confidence interval for ICC or width <0.4).[14] Analysis: Descriptive statistics will be used to summarize measurements for the two sets of evaluators. ICC using a two-way random effects model will be computed to analyze agreement between evaluators. Bland-Altman plots and limits of agreement will be used to further estimate the difference (bias) between the two sets of measurements and generate graphical results.

SA2 – The 50 patients based on Aim 3 precision will be studied. Analysis: Descriptive statistics (mean, standard deviation, percentiles) and coefficients of variation will be generated for clinical evaluation and POCUS measurements. Summary indices based on absolute differences of measurement between the two sets and corresponding 95% confidence intervals will be calculated to quantify POCUS compared to clinical evaluation for each progression measurement (LCEC, SEC, SE, VTE, USE).

SA3 – Sample size and precision for ICC between POCUS compared to clinical or patient assessments:

The sample size is estimated at n=50 during this two-year study based on 30-40 snakebite toxicology consults per year at our three hospitals. An intraclass correlation coefficient of 0.6 or more is expected and the estimated sample size of n=50 from PMH, CMC, and CUH will yield ICC precision of ± 0.18 (half-width of 95% confidence interval for ICC or width <0.4). Analysis: Agreement among progression measurements will be assessed with ICC and Bland-Altman methods. Bias (difference between sets of raters) and 95% confidence intervals will be calculated for each pair of progression measurements.

Equipment Available:

Each of our EDs contain multiple portable ultrasound machines equipped with a linear probe. The PMH ED has the Mindray TE7 model. The CMC ED and CUH ED have similar Sonosite models. Both PMH and CMC utilize QPath software which allows for wireless transmission of ultrasound images to a HIPAA compliant cloud server for further review by our ultrasound trained investigator, Dr. Fields.

Timeline:

Year 1: 2019-2020	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
Specific Aim 1												
Statistical analysis of Aim 1												
Consent and enroll snakebite patients												

Year 2: 2020-2021	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
Consent and enroll snakebite patients												
Statistical analysis of Aims 2 and 3												
Abstract preparation and submission												

Major Limitations

1. There is a modest average of snakebites presenting to a UTSW hospital each year, and these numbers can fluctuate. We are hoping that a two-year timeline will allow for a good overall number of snakebite visits.
2. Most snakebites presenting to our hospital are transfers, meaning that bedside ultrasound evaluation may be later in their course of envenomation. We have tried to create our inclusion criteria to help gather the patients that are early in the course.
3. There are no treatment decisions being made based on the ultrasound evaluation. Patients will likely be a mixture of those receiving antivenom and those who do not. It is unclear if this will be a confounding variable in regards to our 1-hour reevaluation of progression.
4. We have set arbitrary differences that we feel are tolerable for interrater reliability. The 1 cm difference between interrater measurements of percent expansion may be clinically insignificant. In addition, if a greater than 1 cm difference is found between raters, study precision is lost, even if differences may be clinically insignificant.
5. There are logistical challenges in having a second rater be an emergency physician, with needed input at the initial assessment and at the 1-hour reevaluation. The ED may be busy with other critical patients demanding their attention, or the physician who initially made the assessment may be nearing the end of their shift. In addition, patients may be admitted, and could be transported out of the ED before the reevaluation.
6. Due to our recruitment at three hospitals, there will be variability in the ultrasound equipment used. In addition, there may be variability in ultrasound experience by different providers.

References

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