Reviewer's report

Title: Prospective study of recovery from copperhead snake envenomation

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Reviewer: Scott A Weinstein

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Reviewer's report: General

This manuscript reports the results of a prospective, multi-centre observational study of the clinical course of recovery/coalescence of patients envenomed by copperheads, Agkistrodon contortrix ssp. The study addresses an important and little-documented post-envenoming management issue: the follow-up, clinical recovery, and effect of sequelae on the activities of daily living of envenomed patients, as well as the applicability of functional assessment instruments to the assessment of post-envenoming patient recovery. The paper has relevance to those managing the envenomed patient in the acute care setting, but should be of particular interest to those likely to follow patients post-discharge: primary care physicians and physiatrists.

The manuscript does require some minor revision and corrections, although there is one more substantive concern that should be addressed (see ahead). It is to the authors' credit that they appropriately and inclusively list the limitations of their study, but the limited N and subjectivity of many of the instruments used should instil a notable dose of caution when interpreting the broader implications of the study. That being said, this study attempts to assess the important issue of patient recovery after significant crotaline envenoming. Such a patient-centred follow-up investigation is particularly important because morbidity associated with “less severe” crotaline envenomings can have significant effects of the patient and his/her family, as well as an untold productivity loss.

Below, I have made some recommendations and comments, and with some minor editing and addition of some information this well-written manuscript should make an interesting and useful contribution to BMC.

Background

Pg, 4: The cited annual estimate of patients treated in Emergency Departments in the US, 9,000, is an incorrect number! The actual number of weighted native venomous bites in the cited reference is: 2820. This is a commonly incorrectly referenced statistic and must be carefully corrected.

Methods

Participants
While there is recognition of the limitations/challenges in procuring verified identification of the snakes responsible, the lack of formal identification in an untold number of cases does detract from some of the utility of the information, although this is likewise balanced because it is probable that most involved A. c. contortrix.

In this, the geographic locations of the study sites suggest that, barring captive specimens, the majority of the snakes involved were A. c. contortrix (NC), but the case from VA was almost assuredly A. c. mokasen, and although the TX cases are also likely A. c. contortrix, it is peripherally interesting that A. c. laticinctus could have been responsible for envenoming in the relevant region. Although, unlike some Crotalus spp., subspecies of A. contortrix are unlikely to inflict differing severity of envenoming, it is useful to record the most detailed ID possible for the taxa involved.

Although it is a relatively minor issue, if the information is available, I would like to see a specific accounting of the percentage of cases that contained a formal ID.

Data collection

Inclusion is desirable of any specific and relevant data about enrolled patient co-morbidities (e.g. that conceivably may have confounded their clinical progress). Obviously, DM, rheumatism, OA, pre-existing tendonopathies, etc. could play an important role in the recovery from a significant envenoming.

Assessment instruments

Comment: The methods used in assessment of the patients were carefully chosen and likely to yield about as accurate objective information as could be reasonably expected:

However, although sound methodology was used in an inherently challenging study of largely subjective signs/symptoms, I do have a concern about the attempt to verify the responsiveness to study measures (see ahead; this is the main "substantive concern" that I mentioned previously).

Impairment: Disabilities of the Arm, Shoulder and Hand (DASH), etc.

It is to the authors’ credit that they carefully selected appropriate assessment tools for application in this study. Of the validated assessment tools for the upper extremities (UE), DASH is probably the best for evaluating UE pathology that involves multiple joints, and is not relatively limited in comparison to some others (e.g. PRWE) that focus on a given pathology or site (e.g. radial fractures).

Likewise for the use of LEFS, which has been shown to be useful in Spanish and Chinese translation, as well (Cuesta-Vargas et al., 2014; Health Qual. Life Outcomes 12, 75; Hou et al., 2014, J. Formosan Med. Soc. 113, 313-320).

Analysis

Sample size
The limitations are recognised of the circumstances resulting in a small N, but this does compel caution in deriving any broad conclusions from this limited, albeit well-conducted investigation, and a bit more emphasis on this is desirable.

Responsiveness of study measures

This is the material that attracts my “substantive concern”. In my view, there is questionable validity of this understandable effort to assess the responsiveness of the instruments in evaluating clinical change. It should be emphasised that these are calculations using subjective evaluations and may not reflect an objectively factual change or lack thereof in functional limitation(s). It would not harm the utility of the study if these subjective evaluations of inherently subjective scores were deleted.

Results

Subject enrolment

N=20; as noted previously, this is quite a small study although the difficulties and inherent limitations of conducting this study are certainly recognised and appreciated. Still, there must be caution in the interpretation of the findings, and, from my perspective, it would be most helpful if Table 1 included any specific, potentially relevant co-morbidities of the enrolled patients in order to assess if any had confounding factors that influenced interpretation of the results.

Recovery from copperhead envenomation (Comment: please note the suggested edit deleting, “snake”, in the subsection title; this suggested edit is applicable throughout the manuscript after [possibly] one initial use)

Comment: “Only”? This is still the majority, and it is a very subjective question. Suggest deleting “only”.

Health-related quality of life

As considered in previous comments, did any of these patients have relevant co-morbidities that could have influenced their arthropathy or clinical recovery?

Work productivity and daily activity impairment

“….and 2 additional subjects appear to have lost…”.

Suggested edit and comment: “…appeared…”. Did they or not?

Correlation between study measures

The authors’ observations about the influences on the figure of eight measurements are probably correct, and unfortunately significantly decrease the utility of these measurements.

Responsiveness of study measures
See my previous comments re concerns about the inherent subjectivity of these measurements. From my perspective, these are fine if presented as they are, but without any well-intended, but essentially equally subjective, efforts to determine a more objective assessment of their value/utility.

Safety

Comment: It is an aside, but interesting that the Fab acute hypersensitivity incidence recorded in this series of patients was similar to that noted in the early pre-marketing trials of it, rather than the significantly lower incidence noted in later series.

Discussion

Comment: As noted earlier, there is no need to repeat “snake” after “copperhead”.

Figures

Figure 1 is unnecessary and can be deleted. The remaining figures contain some information that could be considered a bit repetitive with the Tables and the text. However, from my perspective, it is useful to include the graphic comparisons of varied performance instruments used to assess clinical progress during convalescence. Thus, even though some of the analyses may be perceived to be repetitive, these all are complimentary to a comprehensive presentation of the results and should be retained.

Tables

Table 1: as I mentioned earlier, I would like to see relevant co-morbidities included, but this could be simply added, as relevant, to the appropriate text. I am especially interested in any pre-existing arthropathy, tendonopathy, moderate-severe OA, etc. should be retained, and a very brief review of the stats suggests that these are sound, although I have not completely back-calculated these. As mentioned earlier, I feel that it is desirable to include a bit more detail about the cases in which the envenoming taxon has been identified.

Also, as mentioned previously, the study sites suggest that, barring captive specimens, the majority of the snakes involved were A. c. contortrix (NC), but the case from VA was almost assuredly A. c. mokasen, and although the TX cases are also likely A. c. contortrix, it is peripherally interesting that A. c. laticinctus could have been responsible for envenoming in the relevant region. Although, unlike some Crotalus spp., subspecies of A. contortrix are unlikely to inflict differing severity of envenoming, it is useful to record the most detailed ID possible for the taxa involved. This is but a mild issue in this well-performed study.

Table 3: Also as mentioned earlier, the question posed (“completely recovered”) is very subjective and of questionable value, aside from determining whether the patient had returned to pre-morbid full spectrum of activities (e.g. such as the
more useful info presented in Table 6).

**Table 5:** Although the pain score is inherently subjective and individually widely variable, I think that another stated limitation of the study is the subjectivity of several self-reported measures (I agree there is no other way to realistically obtain the info, but these should still be conditionally noted as such).

**Table 7:** Question: It is desirable to know a bit more about the patient reporting a “much worse” eval on Day #28 (again, co-morbidities? a significantly more severe envenoming in comparison to the others in the study, etc.)?

**Table 11:** Interesting that a patient reporting a pre-envenoming score of 23.9 eventually showed a higher score on Day #28; any comments from the authors?

**Table 17:** As noted repeatedly, a bit of a seemingly contrived attempt to imbue more “objective” assessment (e.g. calculation) to many subjective measures. I am not certain this is needed or useful, other than as mentioned in text with a comment that it is unclear if it offers a measure of the actual utility or applicability to the actual performance of the instruments used.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests