Author's response to reviews

Title: Prospective study of recovery from copperhead snake envenomation

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Author's response to reviews: see over
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Diana Marshall, Senior Managing Editor
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**Re: Prospective study of recovery from copperhead snake envenomation**

Dear Dr. Marshall,

Thank you for reviewing our manuscript. We found the reviewer’s additional comments to be helpful, and we have incorporated all requested changes. These are presented in tabular form on the following pages.

As before, we have attached a “clean” version of the revised manuscript, and we are happy to provide a “red line” version upon request. The line numbers in our response to reviewer comments refer to the “clean” version.

Thank you for considering our revised manuscript. Please let me know if we can be of any further assistance.

Best regards,

Eric Lavonas, MD
On behalf of the Copperhead Snakebite Recovery Outcome Group
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<th>#</th>
<th>Reviewer Comments</th>
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<td>1</td>
<td>I appreciate the authors’ qualification of my comment re the approximated number of presentations of &quot;venomous&quot; snakebites. I am familiar with the O'Neill et al info, but I disagree that it is clear that the &quot;vast majority&quot; of &quot;unspecified&quot; species were venomous. Many cases present without any verifiable identification of the purported &quot;venomous&quot; species, and should not be accepted as being inflicted by a venomous species when in fact there is no verification of the likely &quot;suspect.&quot; In addition, there is a very undesirable recent sensationalist trend in both research and clinical toxinology that has muddled the definition of &quot;venomousness.&quot; I have consulted on several cases in which a non-venomous species was termed &quot;venomous&quot; because of a notable and disturbing confusion re the biologic definition of venom. With all that said for clarification, I do think the authors provided an acceptable and sensible solution by commenting, &quot;...for evaluation of potentially venomous snakebite.&quot;</td>
<td>We are pleased that the reviewer finds our proposed solution acceptable. No further changes made.</td>
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<td>2</td>
<td>Re the following sentence, a suggested edit: &quot;The vast majority of venomous bites are caused by crotaline snakes (pit vipers: rattlesnakes, cottonmouths, and copperheads).&quot;</td>
<td>The reviewer's suggested edit already appears in the manuscript (lines 71 - 72). No further changes were made.</td>
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<td></td>
<td>As noted in some of my initial comments, it is clear from the sentence, even to those readers unfamiliar with these crotalines, that these are all snakes, and although common names have little utility, the most accurate use for cottonmouth and copperhead does not require, &quot;snake&quot; as an additional identifier.</td>
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| Comment #6 (Discretionary Revision) | This information was provided in the previous revision (lines 343 – 344).

The basis for my comment re possible co-morbidities arose from the vague nature of the authors' comments, "...patients were excluded...if they had a distracting injury or other condition that would limit the ability to make a reliable self-report of functionality status based solely on the condition of interest."

While I agree it raises the issue, it should have some examples of co-morbidities that the authors encountered in enrolled patients that resulted in their exclusion. As simple list of several examples in the Methods would suffice.

In response to the current reviewer comment, we re-wrote the first paragraph of the Results section (lines 337 - 346) to further emphasize this information. We reviewed the screening logs again and confirmed that no subjects were excluded based on this criterion.

In addition:
-- We reviewed the study screening logs again and confirmed that no subjects were excluded based on this criterion.
-- We reviewed the past medical and surgical histories collected at enrollment and confirmed that no subject with comorbidities likely to affect the study outcomes was inadvertently enrolled.
-- We reviewed the study protocol, and confirmed that it did not provide examples of co-morbidities that should result in exclusion. Because the protocol did not provide examples to the site investigators, we are concerned that inserting examples in the Methods section of the manuscript might be misleading.

Comment #25 (Discretionary Revision) | We agree with the reviewer’s point and added language to the discussion section (lines 507 - 514).

The authors seem to have missed the crux of my comment. While I completely agree that there is no other reasonable way for patient-centered reporting of pain, the limitations should be mentioned/cautioned of reporting this highly subjective and personality-influenced symptom. This is a proviso that is commonly included in studies that include pain as a significant part of the presenting complaint.

I will not "press" this point but as I originally commented, I think it is desirable to caution about the wide spectrum of patient variability in the interpretation and reporting of pain/unpleasant sensations.

Comment #26 (Minor essential revision) | Notation of this added to the results section (lines 377 - 382) and on the footnote to Table 7.

The authors include some interesting information re their evaluation of the patient who reported a "much worse" status on Day #28. It might be desirable, as a possible tabular footnote, that this patient's report was (understandably) deemed "anomalous". |