Author's response to reviews

Title: Predictors for Delayed Encephalopathy following Acute Carbon Monoxide Poisoning

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Author's response to reviews: see over
Dear Dr Tim Sands,

Thank you very much for your kind recommendation and advice for our previous manuscript.
We made amendments on our previous manuscript along with the reviewers’ comments, and at the same time, in “Answer to Reviewer” following this letter we listed correction points after reviewers’ comments respectively.

I would be most grateful if you could consider publishing new version of our manuscript for your Journal.
I really appreciate your effort for my manuscript.

Best Regards,

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Answer to Reviewer

Reviewer: Dr Eric Lavonas

Major suggestions:

1) Describe chart review methods. There is no definitive checklist for this (there really should be!), so I usually use the criteria in Gilbert EH et al., Ann Emerg Med 1996; 27(3):305-8.

⇒ On p5, the Methods have been revised as follows:

Patient medical records were retrospectively reviewed, and patients who developed DNS and patients who did not develop DNS were compared in terms of 16 items: gender, age, location of exposure, estimated duration of exposure, whether or not the patient was transported from another hospital, severity of impaired consciousness (i.e., Japan Coma Scale [JCS] score\(^{(10)}\)) when the patient was first seen at a hospital, CO-Hb level when the patient was first seen at a hospital, white blood cell (WBC) count and CK, CK-MB, and LDH levels on the day the patient was seen, whether or not there were abnormal findings from a head CT scan when the patient was first seen, whether or not HBO therapy was administered on the day the patient was seen, diagnostic category according to “Mental and behavioural disorders” in the International Classification of Diseases, Tenth Revision (ICD-10)\(^{(11)}\), duration of hospital stay, and number of sessions of HBO therapy.

2) Define your outcome of interest (DNS) as precisely as possible. It is not clear to me from the writing whether the Global Assessment Scale was used as a predictive variable, part of the outcome definition (used to diagnose DNS), or both. Of course it cannot be both.

⇒ On p9, the Discussion has been revised as follows:

Clinically, the GAS score was independent of the development of DNS, and a lower GAS score was not considered to be a predictor for development of DNS. However, individuals with a lower GAS score may be profiled as individuals with worsening psychiatric symptoms to the extent that they affect physical and social functioning. These individuals may carefully plan to commit suicide by actions such as selecting a location away from public view, sealing up a car or room, and combining multiple methods of suicide. These actions would result in exposure to CO sufficient to subsequently cause DNS.

3) Perform a multivariate analysis. The authors report that abnormal initial head CT, increased circulating levels of CK, CK-MB, and LDH levels, and low GAS scores, but it is unlikely that these are all independent predictors.

⇒ Response to the Reviewer:

We performed multivariate regression analysis but failed to achieve satisfactory results due to missing data. Thus, we did not include results of that analysis in our manuscript.
4) Report clearly the time from onset of poisoning (or initial presentation to care) that each predictive or outcome measure was assessed.
⇒Response to the Reviewer:
The time to development of intermittent CO poisoning has been included in the table.

5) Once you have derived a predictive rule (high risk of DNS, low risk of DNS, or both), apply it to an independent population (validation data set) and report rule performance. If this is not possible, then state clearly that your analysis is hypothesis-generating and independent confirmation is necessary.
⇒The following passage has been added on p10.
The results of this study are tentative. Plans are to collect more substantiating data and conduct additional studies in the future.

6) On page 4, second complete paragraph: The analysis by Hopkins et al. Am J Resp Crit Care Medicine 2007; 176(1): 1001-6 examines both clinical factors and genetic factors (APO-E genotype) that correlate with neurological sequelae 6 weeks following CO poisoning. This is, I think, the closest previously-published manuscript to the current study and warrants inclusion in the discussion.
⇒p4 has been revised as follows.
A recent study examined development of cognitive sequelae and genetic factors 6 weeks after CO poisoning. The study found that the apolipoprotein (APOE) epsilon4 allele was not associated with development of cognitive sequelae.

Additional, less critical suggestions:
7) Background:
In general, I would shorten the background section. Those portions that place the results of the current investigation into context are better located in the discussion section.
⇒Response to the Reviewer:
As the Reviewer’s suggested, references have been added, but shortening the Background section would prove difficult.

8) You accept the premise that HBO therapy decreases the proportion/severity of DSN following CO poisoning, but this remains controversial worldwide. Three of the four articles cited are review articles. Please at least acknowledge the controversy and contradictory results of various clinical trials. The Cochrane review by Buckley et al. (last revised 2011) is a good place to start.
The passage on p3 has been revised as follows:

Previous studies comparing the two therapies have reported that HBO therapy is effective as a treatment to reduce the incidence of DNS and reduce its severity in cases of acute CO poisoning [3,4,5,6]. Other studies, however, have disputed that finding, so there is still worldwide controversy regarding the effectiveness of HBO therapy. In addition, various studies worldwide have cited different criteria for administering HBO therapy during acute CO poisoning due to the ambiguity of indices of the clinical severity of acute CO poisoning. Criteria for administering HBO therapy have yet to be standardized. Moreover, a patient transfer from a medical facility with no HBO chamber to a facility with an HBO chamber has to be considered [7].

9) In the third paragraph, I think the authors are conflating different concepts. CO poisoning exposure can be acute or chronic (in many but not all chronic poisoning cases, the exposure is intermittent). The outcome of this exposure can be recovery (without sequelae) or neurologic sequelae. Neurologic sequelae can develop at the time of poisoning and not go away (persistent neurologic sequelae) or can develop after a delay (delayed neurologic sequelae). Many authors postulate a different mechanism for persistent and delayed neurologic sequelae (ischemia and triggered apoptosis, respectively).

The passage on p3 has been revised as follows:

CO poisoning is generally classified as acute CO poisoning or chronic CO poisoning depending on the duration of CO exposure. CO poisoning is categorized into different forms based on the clinical manifestations resulting from CO exposure over time. With acute CO poisoning, the patient recovers without sequelae, but with delayed CO poisoning or intermittent CO poisoning the patient can be left with neurologic sequelae.

Delayed CO poisoning refers to impaired consciousness that develops at the time of poisoning and that persists without improving. This form of poisoning causes brain cells to be deprived of oxygen and can lead to sequelae such as amnestic syndrome, loss of initiative, affective incontinence, and parkinsonism [8]. Intermittent CO poisoning is thought to develop as a result of the progression of focal demyelination of the cerebral white matter and subsequent neuronal death.

10) Methods: In the first sentence of the methods section (abstract and manuscript), I find it very helpful when authors state the study type and population. e.g.: This is a retrospective cohort study of 79 consecutive patients treated at a single institution for CO poisoning.

Response to the Reviewer:

Wording like that suggested by the Reviewer has been added to the Abstract and to the Methods section in the main text.
11) Results: Rather than report \( p = 0.000 \), report \( p < 0.001 \). Because age has previously been described as a risk factor for poor outcome, it would be helpful (probably in Table 1) to report the number/proportion of patients in each 10-year age group (20 - 29 years, 30 - 39 years, etc.)

⇒Response to the Reviewer:
On p6-7, “\( p = 0.000 \)” has been revised to “\( p < 0.001 \).”

12) It appears that transfer from an outside institution is a significant risk factor for poor outcome. Consider adding this to the multivariate model (if appropriate), or performing a subgroup analysis excluding the transfer patients.

⇒Response to the Reviewer:
The proportion of patients who were transferred from an outside facility has been included in the table.
Of the 19 patients who were transferred, 2 developed DNS. Of the 60 patients who were not transferred, 11 developed DNS. Transfer alone was deemed not to be a risk factor for a poor prognosis.

13) Discussion: Under patient's background and circumstances (third complete paragraph on page 7), you discuss place of exposure in more specific categories than you collected in your study. In general, I would avoid either introducing new results in the discussion section or expanding beyond your results.

⇒Part of the paragraph on p7 has been revised as follows.
The location of exposure was generally classified as in a room at home and in an automobile.

⇒Response to the Reviewer:
Discussing the location of exposure in greater detail proved difficult due to insufficient data.

14) On page 8, first complete paragraph: The commonly repeated statements about COHgb levels and symptoms have been roundly disproven (see Hampson et al., Undersea Hyperb Med 2012; 39(2):657-65). Close examination of the Weaver trial results (2002) corroborates these observations.

⇒Response to the Reviewer:
The passage about CO-Hb levels and symptoms on p8 has been deleted.