Author's response to reviews

Title: Copeptin is associated with mortality and outcome in patients with acute intracerebral hemorrhage

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Version: 2 Date: 20 April 2010

Author's response to reviews: see over
Dear editor, thank you for the careful and detailed reviewers’ comments, which allowed for a considerable improvement of our manuscript. We answered all reviewers’ comments in detail and highlighted changes accordingly in the revised manuscript.

We formatted our manuscript according to editorial request.

**Reviewer’s 1 report:**
I found the study to be complete and able to be understood clearly as written. There were no obvious corrections needed to produce a readable, accurate manuscript.

The study’s greatest limitation is sample size. This is brought forth by the authors in their discussion.

The statistical analysis of the report is sound. The figures support the statistical results.

As the authors state, this is a good preliminary study whose results will need validation with a larger study. Thus, this study is currently very applicable to those who have research interests in the area of bio-marker analysis. If a larger trial is completed which confirms these results, there will be a broader audience for the material presented.

We thank the reviewer for this encouraging comment.

**Reviewer’s 2 report:**
The authors studied the association of copeptin with mortality and outcome in patients with intracerebral hemorrhage. In 40 patients with acute ICH, copeptin level was found to correlate with outcome. The authors conclude that copeptin is a new prognostic marker in patients with ICH.

Major compulsory revisions:
None

Minor Essential Revisions:
1. Please indicate how many patients who died had their care withdrawn by family. If majority of patients died due to withdrawal of care, then the association of copeptin level with mortality is unclear and should be addressed in the discussion.

   Answer: We now added the following sentence in the ‘Results’ section: None of the patients had died due to withdrawal of care (Page 7).

2. Time from symptom onset to time of copeptin determination should be included in the table to determine the impact of delayed diagnosis with copeptin level.

   Answer: We added this information in the ‘Results’ section and we discussed this issue also in the limitation section as follows:

   Results (Page 6 and 7):
   “The time from symptom onset to blood withdrawal for copeptin determination ranged from 2 to 72 hours. For 7 patients, blood withdrawal was done in the first three hours, for 6 patients between 3 and 6 hours, for 7 between 6 and 12 hours, for 9 patients between 12 and 24 hours and for 11 patients between 24 and 72 hours. Copeptin levels were not significantly different between these groups.”

Discussion (Page 10):
“Our study included all patients who presented to the ED within 72 hours after the onset of clinical symptoms, and thus constitutes a heterogeneous population. Due to our limited
sample size, we are not able to assess the time effect in our study. In the aforementioned [1] ischemic stroke trial however, a subgroup analysis revealed no difference in the predictive value of the copeptin level depending on whether it was measured 0-3 hours, 3-6 hours, 6-12 hours, 12-24 hours, or 24-72 hours after symptom onset.”

Reviewer’s 3 report:
The paper “Copeptin is associated with mortality and outcome in patients with acute intracerebral hemorrhage” might be better titled “Copeptin is associated with increased mortality and poor outcome in patients with acute intracerebral hemorrhage”

This study extends the analysis of copeptin concentration in another devastating disease, intracerebral hemorrhage. Although the patient population was small, it represented a significant amount of time and energy in this less common form of stroke. The paper suggests that measuring copeptin concentrations may aid in the ability to prognosticate better in ICH. While I certainly commend the authors on their data, I do not feel that at this stage (or perhaps ever), measuring these concentrations will have much advantage over clinical and radiological evaluation. The authors freely admit that these measurements do no better than the admission GCS or ICH volume. There was also no mention of combined clinical scores such as the Hemphill score.

The concept that this elevation in copeptin may be at least partially based on cerebral edema is intriguing, but there is not evidence presented here that this is the case. Are there animal studies in ICH that support this hypothesis? How might understanding the role of copeptin in ICH help with possible therapeutic interventions? Explore the potential pathophysiological role of Copeptin in ICH more fully. More fully explore the possible therapeutic relevance of this peptide elevation.

Answer: Unfortunately, we did not find any literature about experimental ICH and brain edema specifically related to vasopressin. There is literature about experimental ischemic stroke, subarachnoid hemorrhage and brain injury and the role of vasopressin receptor antagonists. There is also a clinical study about vasopressin and brain edema formation and outcome in head injured patients. We have modified this section in the discussion to more clearly point to the pathophysiologic background and potential therapeutic intervention (page 19):

“Copeptin mirrors circulating vasopressin levels and vasopressin itself may also directly influence the clinical course. Data from experimental studies imply that vasopressin plays a role in brain edema formation as blocking of vasopressin receptors attenuates brain edema in ischemic and traumatic mice models.[2-4] The relationship between vasopressin levels and brain edema development has also been demonstrated in a clinical study of head-injured patients.[5] Brain edema formation predicts an unfavorable outcome in ICH.[6] Therefore, copeptin levels might reflect developing or existing brain edema and might therefore be helpful in identifying patients at risk for brain edema formation who could profit from therapeutic interventions, such as the administration of a vasopressin antagonist.[3] A limitation of our study was that we could not monitor brain edema formation and link it with copeptin values, because imaging studies of the brain were not routinely repeated”.

I would like to see the following included in the manuscript. Include the Hemphill or similar combined scores for ICH prognosis in their Comparison

Answer (Page 5, 8, 9): To compare the predictive value of copeptin with combined clinical features, the ICH Score according to Hemphill [7] and the ICH Grading Scale according to Ruiz-Sandoval [8] was included in our manuscript. Changes were made accordingly in ‘Patients and Methods’, ‘Results’ and ‘Discussion’.
Downplay the role of Copeptin as a possible prognostic marker
Answer: Throughout the manuscript, we changed the wording according to the reviewer’s suggestion.

References