Author’s response to reviews

Title: Development and external validation of a new PTA assessment scale

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Version: 2 Date: 25 June 2012

Author’s response to reviews:

Please find included the answers to the reviewers comments. We would like to thank them for their positive remarks as well.

Reviewer’s reports

Reviewer I
Reviewer: Teneille Gofton

Reviewer’s report:
This manuscript describes the development and validation of a novel tool for assessment of post-traumatic amnesia following traumatic brain injury. It is of interest to those practicing in the field of neurology, neurosurgery, emergency medicine and general family medicine. Overall, the manuscript is written in a clear and concise manner.
Answer: We thank the reviewer for these positive remarks.

Minor revisions:
1. A concern is the difference in the distribution of patients with varying severity of TBI in both the derivation and validation stages of the study. The vast majority of patients fall into the mild TBI group, with only 20% (approximately) of the patients falling into the moderate or severe TBI groups. This begs the question: how applicable is this PTA assessment tool for patients with moderate or severe TBI. It may be beneficial to validate the data in a larger cohort of patients with
Answer: We agree with the reviewer's observation that we eventually included more mild TBI patients than patients from the moderate/severe TBI category. This might have implications for the generalizability of our PTA scale. We have added two comments on this matter at the end of the discussion section (limitations and future research suggestions).

2. Paragraph 2, page 5. Re remembering the examiner's name. The portion of the sentence in this section may be better suited to brackets. Currently, it is difficult for the reader to understand without reading the sentence multiple times.
Answer: We agree with this remark and changed the text accordingly.

Major revision:
3. I am surprised that the institutional review board waived any requirement for consent to participate in the study. Could this be verified?
Answer: Our local/ institutional review board has indicated that for the assessment of questionnaires and the anonymous registration of demographic and clinical data, further evaluation was not necessary. All patients (or initially their next-of-kin), control patients and healthy controls have nevertheless given consent to participate in the study. Please find attached (below) a written statement (English, e-mail) of our institutional review board.

Van: M.vanderVlist@iwkv.umcn.nl [mailto:M.vanderVlist@iwkv.umcn.nl] Namens cmo@iwkv.umcn.nl
Verzonden: maandag 25 juni 2012 9:53
Aan: Jacobs, B
Onderwerp: 2009/113
Title: Development and external validation of a new PTA assessment scale
Bepaling incidentie van afasie bij patiënten na een traumatisch hersenletsel.

Dear mr Jacobs,

On behalf of the research ethics committee of the Radboud University Nijmegen Medical Centre I hereby let you know that the abovementioned study has been carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

Best regards,
On behalf of the CMO Regio Arnhem-Nijmegen
Dr F. Huysmans, Chairman
Universitair Medisch Centrum St Radboud
IWKV - Commissie Mensgebonden Onderzoek
Reviewer II
Reviewer: Sandrine de Ribaupierre

Reviewer's report:
Interesting article.

Major revision:
- it should be made clearer how and when the tests were administered to the patients, because I don't understand how there can be results in the severe TBI (GCS <8) for any of the PTA test, as per definition those patients are in a coma! I suspect that they have a GCS <8 when they arrive but might get better within the first 24h; however I believe that is not clear in the manuscript and needs to be clarified. The exact timing of the test compared to the arrival of the patient in hospital as well as an idea of how fast the patient improved is important.

Answer: We thank the reviewer for this helpful comment. Mild TBI patients were assessed immediately on presentation to the ED, whereas moderate and severe TBI patients were assessed as soon as possible after regaining consciousness and when they were able to cooperate. We have added this information in the Methods section. In the Results section we have added data on the mean number of days post-trauma that elapsed before the moderate/severe patients were included.

For moderate and severe TBI, when was the GCS assessed, and was a low GCS score given because of secondary issues (seizure, meds?) which would explain why the patients were then able to answer appropriately to the test within 48h?

Answer: The GCS score was determined after surgical resuscitation, preferably obtained before sedation and intubation. We have added this additional
information to the Methods section. Falsely low GCS scores, for instance due to medications, could not be excluded completely.

There is also a bias within the education between the different groups (especially with the severe TBI, which cannot be corrected, but maybe could be explicitly stated with its implication)
Answer: We agree with this remark and changed the text accordingly.

Reviewer III
Reviewer: Carolyn Benson
Reviewer’s report:
Well written. Methods and limitations clearly described. Proposed scale very practical for clinical use.
Answer: We thank the reviewer for these positive remarks.

Discretionary Revisions:
Background, Paragraph 2. “in addition, test items that require remembering…” – the structure of this sentence makes it difficult to read
Background, paragraph 2. “three picture memory test” has been shown, instead of “showed”
Answer: We thank the reviewer for these suggestions. We have changed the manuscript accordingly.

Methods, paragraph 2. Extra control group with vascular central nervous system disease. Could you provide more details regarding this control group and why you chose controls with neurological disease versus more orthopedic patients with no neurological issues
Answer: This comment gives us also the opportunity to make a small correction and to include more information: we included 10 patients with a sensorimotor ischemic stroke (without aphasia) and one patient with a benign cerebral tumor. Including orthopedic trauma patients permitted controlling for factors such as pain and traumatic stress (ED setting). By including neurological control subjects we controlled for aspects of admission at a hospital ward due to neurological disease. We have made changes to our manuscript in the Methods and Results sections.

Methods, paragraph 2. Add comma after “dementia”
Methods, paragraph 2. “not included during weekend” or “night shifts”
PTA assessment, paragraph 1. “started immediately post-injury”, I think immediately on presentation to ED is more accurate
Discussion, paragraph 5. I think higher age should be “older” age
We thank the reviewer for these suggestions. We have changed the manuscript accordingly.

Table 2. How is educational level defined?
Answer: The levels are based on the Dutch educational system and the given categories more or less represent the number of years of formal education. We have added the definitions to the legend of Table 2.

Reviewer IV
Reviewer: Andrea Lazosky
Reviewer's report:
Major Compulsory Revisions - None required.
Minor Essential Revisions
Overall, this is a very interesting study and presents an alternate PTA scale that is shorter than others and offers some benefits of the registration and memory for 3 words and eliminates some of the limitations of other scales used.
Answer: We thank the reviewer for these positive comments.
1. Background paragraph 2, the 4th sentence, beginning "In addition, test items that require...." is difficult to understand. It took me a while to sort out what you were saying. Instead of inserting a phrase in the middle of the sentence separated by dashes, I would break this up into two sentences to make it easier to read and I would add to the end of the sentence ".....by different people" just to make it clearer.
Answer: We thank the reviewer for this remark and have changed the text accordingly.
2. Background paragraph 3, the first sentence should say scales, not scale.
3. Subjects paragraph 1, 3rd sentence needs some wording changes. Suggest, "Two control groups for both the derivation and the validation study were recruited, one group of healthy controls and a second control group of patients with isolated traumatic orthopedic injuries who were admitted to the ED and the surgical ward."
Answer: We thank the reviewer for this remark and have changed the text accordingly.
Please clarify why the 2 control groups' data were not presented separately. I saw only one control group in the tables. Which control group was it? What happened to the data from the other control group? Were the two control groups
collapsed into one control group?

Answer: We collapsed the different control groups (healthy controls, orthopedic and neurological controls) for both study cohorts into one large control group. Including orthopedic trauma patients permitted controlling for factors such as pain and traumatic stress. By including neurological control subjects we controlled for aspects of admittance at a hospital ward due to neurological disease. We added this information to the Methods and Results sections.

4. PTA Assessment - what criteria were used for determining when the patient was out of PTA? Does a patient require a perfect score on the new PTA test to be considered out of PTA?

Answer: We have developed a PTA scale that proved to be accurate in discriminating TBI patients in PTA from control subjects. However, we did not specifically focus our study on the criteria that are required to consider a patient as emerged from PTA. Nevertheless, we consider it reasonable to state that two consecutive maximum test results preclude ongoing PTA. This consideration is added to the Discussion section.

Are the patients told the correct answers each time after the testing?

Answer: Yes, except from the memory items, patients are told the correct answer one time if answer was incorrect. This line is added to the Methods section.

Please clarify administration for the three word memory test. It was a bit confusing at what intervals the tests were administered. Different timelines were presented, 5 minutes, 1 hour, 24 hours, 48 hours.

Answer: In the derivation cohort in mild TBI patients the PTA questionnaire was administered as soon as possible after presentation to the ED, whereas in moderate/severe TBI patients were assessed as soon as possible after regaining consciousness and when they were able to cooperate. In both patient groups PTA was assessed each subsequent 24 hours. In the validation cohort one extra assessment was executed one hour after the initial administration. To clarify these procedures we changed the text in the Methods section.

Please clarify, when using your PTA test, when is the first time the patient is tested for recall of the 3 words to pass the test? Immediately following presentation or five minutes later? At one point in your study a recognition trial was given. How is this data used?

Answer: In the derivation cohort recall and/or recognition was tested each subsequent 24 hours; recall/recognition were not tested “directly” after the initial administration. In the validation cohort recall/recognition were also tested 5 minutes after the initial questionnaire assessment (extra), during the extra assessment (see answer above) at one hour and every subsequent 24 hours. To clarify these procedures we changed the text in the Methods section. The recognition data was only used to derive our new PTA scale, the data on
recognition obtained during validation study was not used.

5. Results - Please specify the criteria you used to define low, medium, or high sensitivity and specificity.
Answer: We did not use specific predefined criteria to define low/medium/high sensitivity and specificity. Not all TBI patients suffered from PTA, therefore the sensitivity of most test items proved relatively low (< 25-30%). A specificity of > 90-95% was considered most relevant, a specificity of < 80% was considered to low in the evaluation of specificity versus sensitivity.

6. Discussion - Last sentence of 3rd paragraph starts with "Whereas..." and is a phrase. Suggest linking it with the previous sentence using a coma.
Answer: We thank the reviewer for this comment and have changed the text accordingly.

The only additional comment is that I would like the authors to state what the exact administration and scoring procedures are that they used for their PTA scale, including criteria for being declared no longer in PTA. (see comments above regarding timelines, first time 3 word memory component administered, whether patients are provided with the correct information at the end of each administration, frequency of administrations, etc).
Answer: We agree with the reviewer that the description of our administration procedures has to be as clear as possible. We hope that the changes we have made to our manuscript have improved the readability and clarity of the manuscript and especially the Methods section.