Author’s response to reviews

Title: The Utility of the Brain Trauma Evidence to Inform Paramedic Rapid Sequence Intubation in Out-of-Hospital Stroke

Authors:
Francois Fouche (Pieter.Fouche@monash.edu)
Paul Jennings (paul.jennings@ambulance.vic.gov.au)
Malcolm Boyle (malcolm.boyle@griffith.edu.au)
Stephen Bernard (steve.bernard@ambulance.vic.gov)
Karen Smith (karen.smith@ambulance.vic.gov)

Version: 1 Date: 17 Dec 2019

Author’s response to reviews:

Dear editor and reviewers

We would like to thank the editor and reviewers for taking the time to comment on our manuscript, and for their thoughtful suggestions. I have replied to each comment.

Reviewer reports:

Rishi Nannan Panday, MD, PhD (Reviewer 1): Thank you for allowing me to review this paper. This is a well written paper. However, this paper needs some improvement. We would like to thank Dr. Panday for the helpful comments.

Abstract:

In the abstract sometimes abbreviations are used and sometimes not. Please be consistent with this. if you use you an abbreviation, keep using it consistently throughout the abstract, instead of writing out the word in full later on.

Thank you. We adhered to the convention of using abbreviations, but (according to the convention) we did not start a sentence with an abbreviation, we spelled it out in that case, as per the norm. For example, if we follow the convention of most journals, starting the final paragraph of the conclusions with “Rapid sequence intubation...” is correct. We hope Dr Panday agrees with this.
Introduction:

Line 31: "Any such ..... trial is needed". Please add some more information in your introduction to support this statement.

We agree with Dr Panday, and have added: “If any component of RSI impacts survival differently for TBI compared to strokes, it would follow that RSI itself has a different effect on these two pathologies. If RSI causes dissimilar survival for these two pathologies, this would mean that the RSI TBI evidence-base does not entirely apply to strokes. Any such differences would imply that a stroke RSI trial is needed”.

Methods section, part "selection of cohort": Line 7: please state the definition of each of the mentioned codes

Thank you, we have added: “Instances of stroke and TBI were identified by the Australian modification of ICD10 codes: S06 (Intracranial injury), I60 (subarachnoid haemorrhage), I61 (intracerebral haemorrhage), I62.9 (intracranial haemorrhage [non-traumatic], unspecified) and I63 (cerebral infarction).”

Methods section, part "predictors of outcomes": Line 28: Why was the GCS used instead of an early warning score as a marker of disease severity? Where there no early warning scores that can be used for this purpose?

Thank you, we agree that illness severity scores are very important. We have previously shown that illness severity is critical to adjust for in stroke research of advanced airways. We used GCS as an illness severity score as it was what we had in this dataset. We did not have NIHSS or any early warning score regrettably. Even so, we have shown in this paper that GCS adequately adjusts for prognostic risk: “However, our measures of prognostic risk due to illness severity and comorbidities together predicted survival well with an area under curve of 0.83, which is higher than the 0.75 that would provide evidence of adequate risk adjustment.” Also, in the manuscript we make a case for GCS, we believe it is adequate: “Whilst Glasgow Coma Scale was not specifically designed as a severity score for TBI and strokes, it could be similarly predictive of in-hospital survival as NIHSS for strokes, and has strong prognostic value in TBI.” Ideally we would have access to early warning score, NIHSS stroke scale or other measures of illness severity, but we believe (and hope the reviewer agrees) that we sufficiently adjusted for illness severity.

Methods section, part "definitions": Line 51: Hypotension is often defined as a systolic blood pressure which remains below 90 mm Hg, despite administering fluids. Was this definition one that also included the effect of administering fluids?

Thank you Dr Panday. We did not (and could not) know from our dataset if fluids were administered directly before or after blood pressure measurement. Ultimately, for this study these definitions were not needed, as they were not important for our research questions. We removed these definitions form the manuscript.

Methods section, part "interactions": Line 51-52: On the basis of which data were these medications selected? Please clarify this in the text.
Thank you, we agree and provided reasons for selecting these. Initially, in the methods section we stated “Midazolam, morphine/midazolam infusions, atropine, ketamine and fentanyl were available to aid RSI”. But we did not assess all RSI medications for interaction, for example, ketamine was only given in ≈ 2.5% of RSI for strokes. Therefore the number in the cells of a table would be too low to test for interaction. The same is for other drugs excluded from interaction. We have added: Medications assessed for interaction with TBI and strokes include atropine, midazolam, midazolam/morphine infusions and fentanyl, as only these medications had sufficient data permitted an interaction test.”

Line 53-55: The word "RSI" at the end of this sentence should be removed

Thank you for pointing you the typo, we have removed this.

Lines 58-60: How often were the vital signs at either the first on-scene measurement or the last on-scene measurement missing? Please clarify this in your data.

Thank you, we have stated in figure one that 25,804 (24.1%) outcome or/and covariate missing data. We have added to the limitations discussion “Previous work using this same dataset showed that missingness were clinically insignificant and did not meaningfully impact estimates. As such, no sensitivity analyses for the impact of missing data were conducted. Missing data (in the main model) for variables from which we calculated the changes in vital signs had an average of 5.9% missing from either the first or the last observation on scene”.

Results section, part "demographic factors": Line 50: Was the survival corrected for the charlson comorbidty index? This surely will have influenced survival. Please adjust for this in your results.

We agree with the reviewer that adjusting for comorbidity is essential. We have in fact adjusted for comorbidity by calculating the Walraven-Elixhauser comorbidity score (as indicated in the manuscript methods section and tables), which has been used in two previous publications on advanced airway management in strokes. We believe the Elixhauser comorbidity score is good for our study, as research has shown that it outperforms the Charlson in some settings. Either way, it is at the least comparable in performance to the Charlson. Please see https://bmjopen.bmj.com/content/5/9/e008990

Limitations section: This section should be part of your discussion, preferably after naming the strengths of your study

Thank you for pointing out this oversight. We have removed the limitations headings and added these considerations to the discussion section.

Discussion section: Please take a very critical look at this section. This section misses strengths. Furthermore, you should reflect more on your own results, for example why did some medication had a positive effect whilst others showed no difference. These things are also parts which should be reflected upon in your discussion. Overall much can be improved in this section by reflecting more on your own results, previous studies, adding strenghts etc.

We agree with the reviewer and have added back discussions we had on these interactions. Initially we excluded these because we were concerned that it would make the paper very long and cumbersome to read. We have also additional strengths in the paper.
Mohamed Amine Msolli (Reviewer 2): I thank the authors for this good study

We are indebted to the reviewer for their time and comments. Thank you!

I have two small typo corrections page 3 line 15 "but the evidence from this trial can't be applied" in place of "can be applied"

Excuse the oversight, we have fixed this.

page 3 line 31 "any such differences would imply that a stroke RSI trial is needed" in place of "RSI a stroke RSI trial is needed"

Typographical error, we have fixed this. Thank you!