Author’s response to reviews

Title: Assessment of agreement and interchangeability between the TEG5000 and TEG6S thromboelastography haemostasis analysers: a prospective validation study

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Version: 1 Date: 07 Jan 2019

Author’s response to reviews:

Dear Professor Guangde Tu

Re: Manuscript: BANE-D-18-00039

Title: Title: Assessment of agreement and interchangeability between the TEG5000 and TEG6S thromboelastography haemostasis analysers: a prospective validation study

On behalf of our co-authors, we would like to sincerely thank you for considering our revised manuscript for publication in BMC Anaesthesiology. The comprehensive review and constructive comments provided from the Reviewers have been immensely appreciated.

In response to each Reviewer’s comments, as requested, we have provided the following:

1. Cover letter outlining our point-by-point responses to the academic editor and reviewers. This letter has been uploaded as a separate file and labelled 'BANE-D-18-00039 Response to Reviewers'.

2. A copy of our manuscript highlighting changes made to our original version in RED. This file has been uploaded as a separate file and labelled 'BANE-D-18-00039 Revised Manuscript'.

3. Revised tables, to include the new table 1. This file has been uploaded as a separate file and labelled ‘BANE-D-18-00039 Revised Tables’.

4. A new appendix file, containing the new appendix 1. This file has been uploaded as a separate file and labelled ‘BANE-D-18-00039 Appendix’.

Response to Prof Evan G. Pivalizza (Reviewer 1)

We thank Prof Pivalizza for their expert comments and constructive suggestions. Please find below our detailed point-by-point response.

Reviewer comment 1. “Thanks for the opportunity to review this well described study and well written manuscript of a relevant, current clinical question. Although the power analysis is supportive and you have made appropriate and not over-stated conclusions and recommendations, the small study in context of the very heterogenous population (which you describe as clinically relevant) is noted. Last sentence of methods: indeterminate or missing data? How many were there - can't tell from any of the results or tables?

Authors’ response: Thank you for your positive comments. Regarding your specific question regarding “indeterminate or missing data? How many were there - can't tell from any of the results or tables?” We appreciate the Reviewer’s concerns regarding missing data and for raising this important question. Indeterminate or missing data when secondary to true values being lower than what was recordable were assigned a value of zero, and when secondary to true values being higher than recordable were assigned the maximal value for that parameter, or, for the case of TEG5000 maximum amplitude, measured manually from the graphical representation. Missing data due to failed sample analysis from either the TEG6S or TEG5000 were omitted, and left blank, as per correlation coefficient calculation standards.

Our study encountered only nine incidents where individual TEG parameters were unable to be obtained, out of a 975 data points (<1% total data) and one failed TEG5000 sample analysis (due to a device error). Six individual TEG6S data points failed to obtain a reading. This occurred twice for estimated fibrinogen level (Fib FLEV), twice for fibrinogen maximum amplitude (Fib MA) and twice citrated kaolin lysis levels (CK LY30%). The TEG6S graphs for all of the above data points showed analysis failed because the six readings were extremely small. Subsequently, all TEG6S missing data were assigned values of zero. Three individual TEG5000 data points failed to obtain a reading. This occurred twice for maximum amplitude (MA), and once for alpha angle. TEG5000 maximum amplitude missing data was calculated from measuring the graph. The single TEG5000 alpha angle missing datum was assigned a value of 80 degrees. This has now been reflected in our updated manuscript.

Thank you once again for raising this comment.
Reviewer comment 2: “As you repeatedly point to the clinical relevance of the population and interchangeable results, I would consider adding a comment that although minor differences in some variables were detected (R 0.9 minutes, K 0.4 minutes, angle 1.7 degrees), all variables fell within acceptable normal limits, changes were likely clinically insignificant and even the apparent bias in MA (difference 5.2 mm which you did comment may affect decision making) and difference in LY 30 (0.61%) would not likely impact clinical decision-making if within normal limits. This will reassure readers and device users that statistically significant changes may not imply clinical concern.”

Authors’ response: We agree with this excellent suggestion and have amended our manuscript accordingly. In the text we have now included the following comment “Although minor differences in some variables were detected, all variables measured by TEG6S fell within acceptable normal limits. As such, observed differences between TEG6S and TEG5000 were likely clinically insignificant and even the apparent bias in MA (difference 5.2 mm) and difference in LY30% (0.61%) would not likely impact clinical decision-making if within normal limits.”

Response to Prof Thomas Kander (Reviewer 2)

We thank Prof Kander for their expert comments and constructive suggestions. Please find below our detailed point-by-point response.

Reviewer’s Comment 1. “The inclusion criteria are unclear. Please provide an exact definition of "TEG as part of standard care". What were the exclusion criteria?”

Authors’ response: Thank you for these insightful questions. Patients were eligible for inclusion if they were an adult patient (age >18 years) within our intensive care unit who had an existing arterial line in-situ and required a TEG as part of standard care. Standard care was defined as the prescribing of a TEG as part of routine diagnostic management to provide the clinician with a point-of-care viscoelastic assessment of the haemostatic process to either detect complex coagulopathies, or for directing rational blood product and coagulation factor therapy.

In order to assess TEG6S and TEG5000 performance on patients with a range of coagulation states, no exclusion criteria were imposed. Once patients were enrolled, all samples were run simultaneously across two TEG6S and one TEG5000 device. This has now all been reflected in the manuscript. Agreement within a healthy population, and reproducibility of results was the object of a separate investigation.

Thank you once again for these excellent comments. We have updated and revised the manuscript accordingly.

Reviewer’s Comment 2. Were any patients missed, i.e. how many patients that should have had a TEG taken as "part of standard care" were missed?
Authors’ response: Thank you for this important comment, which in part was also raised by Reviewer 1 above. TEG was conducted by a single skilled operator, over a two-week period in September 2015, between 08h00 and 18h00, excluding weekends. Testing only occurred when both TEG devices were operational. There were no patients that were missed. This has been revised in the methods and results section.

As outlined in our response above, we only encountered nine incidents where individual TEG parameters were unable to be obtained, out of a 975 data points (<1% total data) and one failed TEG5000 sample analysis (due to a device error). Six individual TEG6S data points failed to obtain a reading. This occurred twice for estimated fibrinogen level (Fib FLEV), twice for fibrinogen maximum amplitude (Fib MA) and twice citrated kaolin lysis levels (CK LY30%). The TEG6S graphs for all of the above data points showed analysis failed because the six readings were extremely small. Subsequently, all TEG6S missing data were assigned values of zero. Three individual TEG5000 data points failed to obtain a reading. This occurred twice for maximum amplitude (MA), and once for alpha angle. TEG5000 maximum amplitude missing data was calculated from measuring the graph. The single TEG5000 alpha angle missing datum was assigned a value of 80 degrees. This has now been reflected in our updated manuscript.

Thank you once again for raising this comment.

Reviewer’s Comment 3. “Were all blood samples from unique patients?”

Authors’ response: Thank you for this important question. Patients were only eligible to be enrolled once and all samples were from unique patients, ran simultaneously across two TEG6S and one TEG5000 device. This has been revised in the resubmission manuscript.

Reviewer’s Comment 4. “The authors mention that patients were included consecutively during 7 months (July 2015 to January 2016) but only 25 patients were recruited. Is this really accurate in a tertiary hospital in a large city? Seems as surprisingly few patients.”

Authors’ response: Thank you for this insightful comment. The entire study process including recruitment, sampling, analysis etc. took several months to complete. TEG sampling was conducted by a single skilled operator, over a two-week period in September 2015, between 08h00 and 18h00, excluding weekends. Testing only occurred when both TEG devices were operational. This has been reflected in the manuscript.

Reviewer’s Comment 5. “How many patients or blood analyses were missed due to indeterminate or missing data?”

Authors’ response: Thank you for this comment. All patients who required a TEG during the collecting period were included. There was one failed TEG5000 sample analysis and no violations of the study protocol. The one TEG5000 analysis was missed due to a device error (the cartridge pin dropped prematurely whilst analysing the sample).
As outlined in our response above, we only encountered nine incidents where individual TEG parameters were unable to be obtained, out of 975 data points (<1% total data) and one failed TEG5000 sample analysis (due to a device error). Six individual TEG6S data points failed to obtain a reading. This occurred twice for estimated fibrinogen level (Fib FLEV), twice for fibrinogen maximum amplitude (Fib MA) and twice citrated kaolin lysis levels (CK LY30%). The TEG6S graphs for all of the above data points showed analysis failed because the six readings were extremely small. Subsequently, all TEG6S missing data were assigned values of zero. Three individual TEG5000 data points failed to obtain a reading. This occurred twice for maximum amplitude (MA), and once for alpha angle. TEG5000 maximum amplitude missing data was calculated from measuring the graph. The single TEG5000 alpha angle missing datum was assigned a value of 80 degrees. This has now been reflected in our updated manuscript.

Reviewer’s Comment 6. “When were blood samples taken? Directly after admission or just before discharge or at random. It would make sense to identify a point in time when the TEG values were expected to be as pathological as possible. Was this done?”

Authors’ response: We thank the reviewer for their comment, and agree that it makes sense to perform analysis when TEG values were expected to be most pathological. In our experience, it is often unpredictable when patients have the most profound derangements in their coagulation profiles. We performed the TEG as part of routine diagnostic management when the treating clinician ordered a TEG as part of a point-of-care viscoelastic assessment of the haemostatic process to either detect complex coagulopathies, or for directing rational blood product and coagulation factor therapy. As already alluded, in our responses above, in order to assess TEG6S and TEG5000 performance on patients with a range of coagulation states, no exclusion criteria were imposed. All samples were taken from patients within 72 hours of their hospital admission. These changes have been made to the resubmission manuscript.

Reviewer’s Comment 7. “Where there any patients on anticoagulation treatment during sampling?”

Authors’ response: Thank you reviewer for this important comment. During the testing period, there were no patients on therapeutic anticoagulation therapy including novel oral anticoagulants (direct thrombin and factor Xa inhibitors), warfarin, or heparin. This has been included in the revised manuscript.

Reviewer’s Comment 8. “I miss a detailed description of the included patients”

Authors’ response: Thank you reviewer for this important comment. We have provided a revised Table 1 outlining the baseline patient characteristics.

Reviewer’s Comment 9. “What was the coefficient of variation (CV) for the tests in your laboratory?”
Authors’ response: Thank you reviewer for this important question.

Please find attached a new, complete table documenting the coefficient of variation for the tests in our laboratory. This has been referenced in the revised manuscript and attached as an appendix.

Once again, we are very appreciative of both Reviewers for taking the time to review our manuscript and provide us with extremely constructive feedback. We are grateful for the opportunity to resubmit our revised manuscript for publication in BMC Anaesthesiology.

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