Author's response to reviews

Title: Tracheostomy in septic and non-septic patients can be performed without bleeding complications in case of normal thromboelastometry results (EXTEM CT) despite increased PT-INR: a prospective pilot study

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Author's response to reviews: see over
Dear editor,

We have been advised by Critical Care editors to send our article to your journal with responses to reviewer comments. So here we send a new version of article /responses in red are for reviewer 2 and blue are for reviewer 1/ and would like to publish it in your journal. The other requested thing is clinical trial registration number:

However, our study is purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) and thus does not require registration according to Clinical Trials Registration, http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

Related: Clinical Trials Registration within Recommendations

What is the ICMJE definition of a clinical trial?

Editorials on trial registration at www.icmje.org discuss the evolution of the ICMJE definition of clinical trials. In June 2007 the ICMJE adopted the WHO’s definition of clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration. The ICMJE member journals implemented the expanded definition of clinically directive trials for all trials that began enrollment on or after 1 July 2008. Those who are uncertain whether their trial meets the expanded ICMJE definition should err on the side of registration if they wish to seek publication in an ICMJE journal. The ICMJE secretariat office is unable to review specific studies to determine whether registration is necessary. If researchers or others have questions about the need to register a specific study, they should err on the side of registration or consult the editorial office of the journal they wish to publish the study in.

We declare that the article has not been published, submitted, or accepted for publication elsewhere and that there are no conflicts of interest and that article is of our own work.

Best regards,

Miroslav Durila
Reviewer's report
Title: Thromboelastometry (ROTEM-EXTEM) predicts bleeding complications better than prothrombin time test (PT-INR) during tracheostomy in septic and nonseptic patients: a prospective pilot study
Version: 2
Reviewer number: 2
Referee's comments to the author(s)
Only this section of the report will be returned to the authors. Do not comment in this section on the interest/importance level of the manuscript, or whether or not the manuscript should be accepted.

General comment:
The authors report in their prospective pilot study the limited value of INR to predict bleeding in 119 ICU patients undergoing surgical tracheostomy. In all patients with an increased INR but normal CT in EXTEM (rotational thromboelastometry) surgical tracheostomy could be performed without any bleeding complication. Therefore, the results of this study may contribute to avoid inappropriate prophylactic FFP transfusion in this setting.

Comments in detail:

Introduction
Page 3, line 15: Change “strength of coagulum” to “clot strength”.
Done.
Page 3, line 17f: Change wording to “Rotational thromboelastometry (ROTEM) as a viscoelastic method may be a better method …”.
Done.
Page 3, line 23: Change “consumption” to “transfusion”.
Done.

Methods
Page 4, line 9: ROTEM EXTEM (Tem International GmbH, Munich, Germany) … Suggested changes done.
Page 4, line 10f: What do you mean with normal ROTEM results. Did you consider EXTEM CT, only, or normal CFT, alpha-angle, clot strength (A5, A10, MCF), and lysis parameter (LI30, LI60, ML), too? As far as I understood your study protocol, prolonged EXTEM CT (> 80s?) has been used as an indication to transfuse FFP, only. How many FFP has been administered in this situation in order to correct coagulopathy? Did INR and/or EXTEM CT change after FFP transfusion? Since hypo- and hypercoagulability is mainly characterized by decreased or increased clot strength, these ROTEM results should be reported in a table, too.
Data are added, including CFT, alfa angle, A, MCF, LI30, LI60, ML. Yes, if all parameters were in normal range but CT, then 4 FFP was administered and no control was done afterwards. /discussed also in discussion/ Table 1 is also created.

Page 4, line 14: (i) surgeon performing tracheostomy assessed bleeding as major or non-standard, …
Done.

Results
Page 5: line 8: What was the mean INR and range in the group with INR >= 1.3? (INR min 1.3, max 1.84, and median 1.48), addend in results section
Were there any patients with an INR > 2 or 2.5?
No.

Page 5, line 10 and line 20: INR value between 1.2-1.3 should be changed to 1.21-1.29 throughout the whole manuscript because INR of 1.2 belongs to the subgroup INR <= 1.2 and INR of 1.3 to the subgroup INR >= 1.3.
Done.

Page 5, line 14f: Here, you state that tracheostomy was performed safely without any bleeding complication in patients with normal ROTEM results. First, you analyzed EXTEM test, only. Therefore, you should change “ROTEM results” to “EXTEM results”. Second, EXTEM CT only represents a small part of EXTEM results. As mention before (page 4, line 10f), the other EXTEM results should be reported, too. Here, I suggest to add two tables providing EXTEM CT, CFT, alpha-angle, A5, A10, MCF, Li30, Li60, and ML for patients with INR 1.21-1.29 and INR >= 1.3 as well as for septic and non-septic patients. Since hypo- and hypercoagulability is mainly characterized by decreased or increased clot strength, these ROTEM results may be even more important in predicting bleeding than EXTEM CT (additional references: Davenport R, Manson J, De’Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med 2011;39:2652-8; Adamzik M, Langemeier T, Frey UH, et al. Comparison of thrombelastometry with simplified acute physiology score II and sequential organ failure assessment scores for the prediction of 30-day survival: a cohort study. Shock 2011;35:339-42; and Dimitrova-Karamfilova A, Patokova Y, Solarova T, et al. Rotation thromboelastography for assessment of hypercoagulation and thrombosis in patients with cardiovascular diseases. J Life Science 2012;6:28-35). Can you provide platelet count and plasma fibrinogen concentration for these patients prior to surgical tracheostomy, too? Furthermore, septic patients are characterized by hypofibrinolysis (LI 60 > 96%), too (Brenner T, et al. 2012 (ref 2), Adamzik M, Eggmann M, Frey UH, et al. Comparison of thromboelastometry with procalcitonin, interleukin 6, and C-reactive protein as diagnostic tests for severe sepsis in critically ill adults. Crit Care 2010;14:R178; and Müller MC, Meijers JC, Vroom MB, Juffermans NP. Utility of thromboelastography and/or thromboelastometry in adults with sepsis: a systematic review. Crit Care 2014;18:R30).
Data are completed in table 1 /requested 2 tables are put in one. Also we changed ROTEM to EXTEM, as requested.

Page 5: Did INR and/or EXTEM CT or any other ROTEM parameter change after FFP transfusion? How many FFP has been transfused?
We did not check it again after FFP.

Discussion
Page 6, line 6: Delete “paradoxical”.
Done.
Page 6, line 7ff: Change the wording to “However, in inflammation and sepsis hypercoagulation can quickly change to hypocoagulation, while PT-INR remains unchanged.”
Done.

Page 6, line 9: Change wording to “As PT-INR does not take into account all coagulation factors, …”
Done.

Page 6, line 9ff: Clot strength (A5, A10, MCF) and lysis parameter (LI30, LI60, ML) should be discussed here, too (see comment on page 5, line 14ff and additional references). Recently, Greene et al. published data demonstrating that thromboelastometry measures of clot firmness (EXTEM A10, A20, and MCF) are superior to platelet count in predicting bleeding in patients with severe thrombocytopenia (Greene LA, Chen S, Seery C, et al. Beyond the platelet count: immature platelet fraction and thromboelastometry correlate with bleeding in patients with immune thrombocytopenia. Brit J Haematol 2014;166:592–600). 
Discussed:
Our results of EXTEM say that if parameters such as CT, CFT, alfa angle, A10, MCF, LI30, LI60, ML are in normal range or hypercoagulable, surgical procedure such as tracheostomy can be done safely. These findings are similar to recently published data of Greene et al. demonstrating that thromboelastometry measures of clot firmness (EXTEM A10, A20, and MCF) are superior to platelet count in predicting bleeding in patients with severe thrombocytopenia [14]. Our finding of decreased fibrinolysis in septic patients in later fibrinolysis represented by LI60 and ML is accordance with similar results of Amazik at al. [15].

Changes done and also some discussion added.
Page 6, line 24, page 7, line 2 and 10: INR value between 1.2-1.3 should be changed to 1.21-1.29 throughout the whole manuscript because INR of 1.2 belongs to the subgroup INR <= 1.2 and INR of 1.3 to the subgroup INR >= 1.3. Done in all text.

Page 6, line 12: Change “the rest 40%” to “the residual 40%”. Done.


(Fig. 3). This increase in INR value might be due to the presence of sepsis with increased tissue factor expression on circulation monocytes[15, 19, 20] and this cannot be detected in plasmatic coagulation tests such as PT-INR since the cells are removed by centrifugation, however, CT in ROTEM can be shortened in this case.

Page 6, line 20f: The limitations of the study should clearly be discussed, here. Done.

None of the patients included in this study showed any bleeding complication. Therefore, it can be concluded that surgical tracheostomy can safely be performed if ROTEM results are normal even in case of increased INR (range?). However, the conclusion that thromboelastometry better predicts bleeding complications than PT/INR cannot really be drawn since no bleeding complications occurred in the whole study population. Therefore, I recommend to change the title to “Tracheostomy in septic and non-septic patients can be performed without bleeding complications in case of normal thromboelastometry results (EXTEM CT) despite increased INR: a prospective pilot study”. Title changed accordingly.

Key messages
Page 8, line 15: Change wording to “By appropriate assessment of global hemostasis unnecessary FFP transfusion can be avoided.” Done.

List of abbreviations
Page 8, line 18: Change wording to “CT – coagulation time (time from starting the
test until a clot firmness of 2 mm is reached)

Done.

Page 8, line 19: ESA – European Society of Anaesthesiology Done.

Page 8, line 19: EXTEM – thromboelastometric test with extrinsic activation by tissue factor Done.

References
Page 11f: Additional references as mentioned in the comments, before Done.

Tables and figures
Page 13ff: On the one hand, two additional tables providing EXTEM CT, CFT, alpha-angle, A5, A10, MCF, LI30, LI60, and ML for patients with INR 1.21-1.29 and INR >= 1.3 as well as for septic and non-septic patients should be added (see comment on page 5, line 14ff). On the other, the results presented in figure 1-3 are already presented in the results section. Therefore, an additional presentation as figure is not necessary or can be even condensed in 1 figure. Added table 1.
Reviewer's report

Title: Thromboelastometry (ROTEM-EXTEM) predicts bleeding complications better than prothrombin time test (PT-INR) during tracheostomy in septic and nonseptic patients: a prospective pilot study

Version: 2

Reviewer number: 1

Referee's comments to the author(s)

Only this section of the report will be returned to the authors. Do not comment in this section on the interest/importance level of the manuscript, or whether or not the manuscript should be accepted.

This study employs two coagulation activity assays: ROTEM-EXTEM thromboelastography (TEG) of whole blood, and automated plasma prothrombin time with results expressed as international normalized ratio (INR). Patients with INR > 1.3 (max. 1.84; median 1.48) were tested via ROTEM-EXTEM and all but one had clotting time results within normal ranges (they do not report the INR for that particular patient). That patient was given FFP prior to tracheostomy, which was performed on the rest without bleeding complications. The authors conclude that ROTEM-EXTEM is a better predictor of surgical bleeding complication than PT-INR.

Major comments: There is no mention of PTT and other standard blood clotting parameters such as platelet counts that clearly influence bleeding.

Added in the text of methods.

Kobe, Japan). Arterial blood was used for this analysis. In the cases where INR was prolonged over 1.2, while the platelets count was higher than 50×10^9/L and activated partial thromboplastin time (aPTT) was normal,

Both PT-INR and ROTEM-EXTEM employ a high concentration of tissue factor (TF) to drive rapid coagulation of recalcified plasma or blood, which greatly reduces their sensitivity to variables that can affect coagulation. For example neither can detect severe hemophilia, and the PT is insensitive to the effects of platelet deficiency/malfunction – as is ROTEM-EXTEM if only the clotting time is considered. This is why, as the authors mention, it is generally recommended that physicians not consider “correcting” an INR less than 1.5 prior to surgery – and even then they should consider what specific variables may be influencing the result. Nevertheless, the authors insist on describing INR > 1.2 as “prolonged” with regards to surgical bleeding susceptibility, and then proceed to characterize this interpretation as being less useful than the results of ROTEM-EXTEM, where they rely on normal ranges that have not been validated for assessment of surgical bleeding risks. Indeed no reason is given for why the results of ROTEM-EXTEM are relevant to such an assessment, and its relative insensitivity compared to other TEG modalities (e.g. assays without TF) would appear to make it one of the least useful in this regard. As a result of these
interpretative and methodological decisions, the analysis presented in this MS has little to say about the relative usefulness of either assay in situations where a therapeutically meaningful bleeding risk may actually exist. We used EXTEM because it says about external pathway of coagulation as PT-INR. It is true that there is no data for predicting bleeding on the base of ROTEM. That is why we changed the title and it is also a pilot study.

Minor comment: all of the data in Figures 1-4 could be summarized in a table to convey the same information in much less space. Data in Fig.4 might merit a graph if normal ranges were included for comparison, and if a similar analysis was done for other TEG parameters to aid in the evaluation of global clotting activity.

We believe that figure is more illustrative, so for now we decided not to put them in tables.

Normal values are added to table 1. Legend.