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

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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”.

Page 3, line 17f: Change wording to “Rotational thromboelastometry (ROTEM) as a viscoelastic method may be a better method …”.

Page 3, line 23: Change “consumption” to “transfusion”.

Methods

Page 4, line 9: ROTEM EXTEM (Tem International GmbH, Munich, Germany) …

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

Results

Page 5: line 8: What was the mean INR and range in the group with INR $\geq 1.3$? Were there any patients with an INR $> 2$ or $2.5$?

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 $\leq 1.2$ and INR of 1.3 to the subgroup INR $> 1.3$.

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 tables providing EXTEM CT, CFT, alpha-angle, A5, A10, MCF, LI30, LI60, and ML for patients with INR 1.21-1.29 and INR $\geq 1.3$ 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 procaltitonin, 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, Jufermans NP. Utility of thromboelastography and/or thromboelastometry in adults with sepsis: a systematic review. Crit Care 2014;18:R30).

Page 5: Did INR and/or EXTEM CT or any other ROTEM parameter change after FFP transfusion? How many FFP has been transfused?

Discussion

Page 6, line 6: Delete “paradoxical”.

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

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

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).


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.

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

sepsis. Anesthesiology 2013;118:123-33). Notably, tissue factor expression on circulating monocytes cannot be detected in plasmatic coagulation tests such as PT-INR since the cells are removed by centrifugation, here.

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

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

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)

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

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

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

Tables and figures
Page 13ff: On the one hand, two additional tables 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.