Reviewer's report

Title: Activated coagulation time vs. intrinsically activated modified rotational thromboelastometry in assessment of hemostatic disturbances and blood loss after protamine administration in elective cardiac surgery: analysis from the clinical trial (NCT01281397)

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Reviewer: Daniel Unic

Reviewer's report:

Petricevic and colleagues present results of their study on assessing two point of care devices for assessment of hemostatic disturbances and blood loss after protamine administration in elective cardiac surgery, a topic of interest in everyday clinical practice.

The manuscript is well organized and written (with minor spelling errors). However, there are several issues I think the authors should address before a decision for publication could be made:

MAJOR COMPULSORY REVISIONS:

1. The title states that the article analyzes patients from a clinical trial NCT01281397. At least a brief description of the trial should be presented in the methods section, particularly with clear exclusion criteria.

Also, a trial was supposed to include 400 patients and this study includes 148. Was that a portion of the study cohort and during which period of the trial were the patients investigated (initial, mid, or late)?

2. Chest tube output (CTO) is an obvious end point chosen. Excluded from the study were patients "requiring surgical exploration for excessive bleeding due to obvious surgical bleeding with a bleeding vessel identified". The number of such patients (if any) in the cohort was not given in the results section and 148 consecutive patients recruited leave the impression that no surgical exploration was necessary in this cohort. That should be pointed out (if that is the case in fact).
3. Patients categories for analysis were determined according to the CTO where the "bleeder" category was determined as the amount of CTO above the 75th percentile which turned out to be >1500 mL. No bleeding dynamics was reported or any criteria on how was this (fairly significant amount of CTO) distinguished from surgical bleeding requiring reexploration (criteria on the amount of CTO for surgical bleeding were not mentioned either). This should be better elaborated.

4. Since tranexamic acid was administered routinely at the induction of anesthesia and after protamine administration, its potential effect on results should be discussed.

5. As for the management of postoperative bleeding, it appeared to be left to the clinical judgement of anesthesiologist. As the results show, all blood products were applied. But again, only PRBC and FFP had predetermined criteria for application. A more clear insight might be warranted.

6. Patients in the bleeder category had significantly longer CPB times and lower body temperature on CPB. Effects of both on postoperative bleeding should be discussed.

7. Part of the discussion in which the authors propose a TEM guided algorithm of postoperative blood components administration should be left out completely as it is not substantiated by the parameters investigated in this study. Similarly, parts of the conclusion section not pertaining to the topic of investigation e.g. "Concomitant use of InTEM and HepTEM tests enables precise detection of low to moderate heparin concentration [13]. Therefore, TEM test also enables physician to detect or prevent protamine excess resulting from empirical or ACT-based additional protamine administration. Hemostatic disturbances after adequate heparin-protamine neutralization management may be easily
detected with additional use of ExTEM and FibTEM assays. This may be very useful, especially in patients who developed the coagulopathy due to other CPB associated factors. In such a cases, detection of coagulation factor depletion, platelets and/or fibrinogen dysfunction may lead to appropriate, “targeted” hemostatic therapy and more efficient hemostatic management. Such an approach may help to improve clinical outcome with lower incidence of excessive bleeding, lower transfusion requirements with lower incidence of transfusion related adverse outcomes. Appropriate cut-off’s for transfusion management guided by TEM should be directed according to cut-off’s defined through prospective non-interventional studies" or " In our study the attending clinicians, both the anesthesiologists and surgeons were blinded to InTEM results, therefore administering procoagulant blood products mainly on the clinical grounds. The use of procoagulant blood products certainly affected the amount of bleeding. This decrease in amount of bleeding would reduce the degree of correlation between blood loss and both ACT and InTEM parameters by reducing the sensitivity of each parameters. Although regularly used in clinical practice, ACT lacks to provide prediction of bleeding events. TEM InTEM test was shown to be superior over ACT in assessment of bleeding extent. In addition to, it may be used for heparine-protamine management by concomitant use of Heptem and titration of clotting time parameters which are influenced by either heparin and protamine. MCF parameters significantly correlate to amount of chest tube discharge." should be in discussion section although I think they are out of scope in this investigation. Furthermore, it is unusual for a Conclusion section to include references.

8. In the Conclusion section of the Abstract I find the statement " With aim to predict and prevent excessive postoperative CTO, as well as excessive transfusion requirements, hemostatic interventions with timely and targeted blood component therapy according to TEM results should be considered" beyond the scope of the investigation, at least as the objectives are set.

MINOR ESSENTIAL REVISIONS

1. In the results section of the Abstract results pertaining to the topic of investigation should be elaborated (within word limits). CPB time or temperature should be left for the results section of the text.

2. Tables look very busy! In Tables 1a and 1b, data should be reorganized in such a matter to show continuous data as average with STDEV or median, and categorical data should be presented with number and percentage (just the positive value). In Table 2, groups should
be more clearly labeled than < and >75 perc (eg: bleeder, non-bleeder). Data should be presented as average with STDEV.

3. Figures could be merged into one with legend on the side.

4. Abbreviations should be used consistently throughout the text. Eg. "ROC curves were constructed to assess the ability of ROTEM....". This was the first mention of ROTEM. It should be TEM as throughout the text.

5. There are some typos in the REsults section: "Table 1a and 1b" Should read "Tables"; "thus cut-off" should be "thus a cut-off"; "Median 210 sec vs 192 sex" should obviously be "192 sec"

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests