Author's response to reviews

Title: Transfusion of Fresh Frozen Plasma in non-bleeding ICU patients: TOPIC TRIAL rationale and study design

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Author's response to reviews:

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Amsterdam, November 30, 2011

Subject: Transfusion of Fresh Frozen Plasma in non-bleeding ICU patients: TOPIC TRIAL – rationale and study design

Dear editors,

We thank you for your comments on our manuscript “Transfusion of fresh frozen plasma in non-bleeding ICU patients: TOPIC trial”.

Hereby we resubmit the revised manuscript and address compulsory revisions.

ABSTRACT
- In the methods section we addressed that the TOPIC trial is a non-inferiority trial.

METHODS
- Clinically overt bleeding is further defined as a decrease of haemoglobin >1 mmol/L, bleeding requiring transfusion or hemodynamic instability due to bleeding.
- Time zero in the experimental group is the t=0 blood draw before one of the predefined interventions is performed.

- As a single intervention is studied, which will only be performed after informed consent is obtained, further patient compliance in this study is not relevant. A patient can of course withdraw consent to use the samples for analysis, which is then classified as protocol drop out.

- A sentence is added to the section of “protocol drop out”, here we address that collected data will be used for the intention to treat analysis, unless a patient requires her/his data to be discarded.

- Concerning non-compliance, please see above.

- Although not explicitly stated in the manuscript, we do collect data on other co-interventions, we register transfusion requirements (plasma, red bloodcells, thrombocytes, fibrinogen) the first 24 hours and after 28 days. Furthermore the use of procoagulant medication (e.g. tranexaminic acid, recombinant factor VII) is registered the first 24 hours.

- Data on the fluid balance is available through the patient data management system.

- If a patient that participates in the study needs to undergo a procedure that influences coagulation in the first 24 hours, the patient remains in the study. The primary end point bleeding still will be assessed. The possible required extra transfusion of plasma or other blood products and its reason will be registered. We believe that this represents daily practice on the ICU; therefore these patients should not be excluded.

- The primary end point is procedure related bleeding, this will be assessed by a physician who is blinded for the randomisation result. Assessment of bleeding will be made 1 and 24 hours after the procedure. This is now added to the manuscript.

- PEEP score has been changed in level of PEEP (cm H2O)

- According to the definition, circulatory overload can be defined as bilateral edema on chest x-ray and a wedge pressure >18 mmHg. In patients who will not have a SwanGanz catheter in place, circulatory overload will be defined as pulmonary edema in the presence of at least 3 of the following: positive fluid balance, elevated central venous pressure, a history of heart failure and increase in oxygenation in response to diuretics. Distinguishing circulatory overload from TRALI will be done using the consensus TRALI criteria (worsening acute lung injury within 6 hours after transfusion, with bilateral infiltrates and with no hemodynamic evidence of heart failure). This is now added to the manuscript.


- We thank the reviewer for his suggestion to do a per protocol analysis as well an intention to treat analysis. We added a sentence to the statistical analysis
MINOR ESSENTIAL REVISIONS

- Acronym TOPIC is defined in the abstract.
- Costs is removed from the method section in the abstract.
- Section “study end point” 4th line: 1,2 mmol/L is changed in 1.2 mmol/L
- Section “study end point” acronym PDMS is defined
- Section “statistical considerations” “margin of 0.03” has been changed in “a safety margin of 0.03”
- Page 12 1st line, RCT has been defined.
- 5 keywords have been added: randomized clinical trial, TRALI, coagulopathy, INR, prevention.

We hope that the manuscript after this revision is now suitable for publication in Trials.

Yours sincerely,

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