Author's response to reviews

Title: Prothrombin Complex Concentrate in the Reduction of Blood Loss during Orthotopic Liver Transplantation: PROTON-trial

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Author's response to reviews:

Dear Editor,

We thank you for considering our manuscript for BMC surgery.

Please find enclosed in the resubmission of our manuscript of the study protocol of the PROTON-trial: ‘Prothrombin complex concentrate in the reduction of blood loss during orthotopic liver transplantation’.

Also, below we have listed our point-by-point answers to the reviewer and changes made in the manuscript:

With regards to reviewer 1: No remarks or questions were given by this reviewer

With regards to reviewer 2:

1) Transfusion guidelines for FFP are provided on page 7 of the manuscript. We have highlighted this section. The investigators of all participating centers agreed to transfuse FFP only in case of hypocoagulability on the TEG/ROTEM device in combination with ongoing bleeding.

2) Transfusion of colloid/crystalloids: We have decided not to make guidelines for this study for transfusion of non-hemostatic fluids since all the participating centers follow a very restrictive transfusion and fluid infusion protocol to maintain
low portal pressure and we do not believe that there will be large differences between the centers in fluid infusion and certainly not between the intervention and placebo arm.

3) We agree that transfusion requirements of centers vary greatly and also centers may have different transfusion requirements now then a few years back. It is well know that differences in transfusion requirements between centers are largely related to the local transfusion policy. Therefore, for this multicenter study we have specifically selected centers that are using a similar (restrictive) transfusion policy and have similar mean RBC transfusion requirements in their recent transplant patients.

Indeed, we have previously reported lower transfusion requirements than a mean of 8 RBC, a number we have used in the sample size calculation. However, we have experienced an increase in RBC transfusion requirements in the past few years, possibly related to higher MELD scores, more non-heart beating donation, or even the discontinuation of aprotinin. However, these numbers do represent the mean RBC requirements seen in our center and the other participating centers have confirmed similar transfusion requirements. Before we include a new center to this study, of course transfusion requirements must be compared to avoid large differences between the centers. In other words, this figure does represent the current RBC transfusion requirement in the participating centers. To control for any small differences between the centers we have decided to stratify per center during the randomization.

4) We understand your concern but we do not believe that there will be great differences in preoperative Hb-value between the two arms. Currently the randomization is stratified per center and also for gender and for age, we have added this information to the manuscript. The preoperative Hb-value should have the same distribution between both arms. Also, we want to point out that not all studies find preoperative hemoglobin as a predictor for blood loss during OL, for example:


5) Because of the short half-life of the coagulation factors in Cofact we do not believe the drug to be active after 30 days and we do not believe that any retransplantations occurring after this time point will be relevant to our study. Therefore, we have decided to only follow the patients for 30 days. However, we can still perform a post hoc analysis after 1 and 3 years to analyze patient and graft survival.

We hope that you will find our manuscript suitable for publication in its current form.

Yours Sincerely,
Professor R.J. Porte, M.D. Ph.D., surgeon
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The Netherlands