PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Thromboelastography-guided blood transfusion during cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: study protocol for a prospective randomized controlled trial
AUTHORS	Wang, Shaoheng; Zhang, Qing; Chen, Linfeng; Liu, Gang; Liu, Peng fei

VERSION 1 – REVIEW

REVIEWER	Peter Cashin Uppsala University
REVIEW RETURNED	26-Jul-2020

GENERAL COMMENTS	Thank you for the opportunity to review this protocol for a randomized trial. Here are a few comments. 1: exclusion criteria anemi. Many patients are slightly anemic. Is there a cut-off for the anemia? If any anemia is excluded then there might be a significant fallout of patients making the generalisablilty difficult. 2: Long term anti-platelet therapy – please specify if low-dose acetyl salicylic acid counts as anti-platelet therapy. 3: You may need to specify what is meant with anti-coagulant and anti-platelet therapy - what medications does it include. 4: For clarification - all patients with a history of thrombosis will be excluded? 5: Page 13 – I don't think that patients should be excluded due to hypotensive shock or other severe intraoperative adverse event. It may be prudent to switch infusion/transfusion strategi accordingly in order to manage the situation according to best practice. However, I think it is important to keep the patient in the study follow-up. It is these situation that are important to know the outcome. This was a well-planned and well-written protocol for a randomized trial. Certainly an important subject. I want to qualify my review somewhat as I am not an anesthesiologist, thus I think it may be of importance that further review by an anesthesiologist is performed for better detailed input. Thank you!

REVIEWER	Chukwuemeka Ihemelandu MedStar Georgetown University Hospital, USA
REVIEW RETURNED	09-Aug-2020

GENERAL COMMENTS	Well thought out trial to address an unmet need in cytoreductive surgery a few minor comments: page 12 line 37: Total blood transfusion between 0 and 72 hours after surgery: Within 0-72 hours after the operation, patients will again receive a blood transfusion, including the total amount of RBCs, FFP and PLTs. Could the authors clarify this statement; does this mean that all patients will get a blood transfusion after 72 hrs Page 12 line 45: Patients who need a second operation due to postoperative bleeding within 72 hours will be excluded from this study. Why the exclusion of these patients Page 13 line 5: If the condition progresses to severe intraoperative adverse events, such as shock, heart failure and massive blood loss, the patient will be excluded from the study. Again why exclude the patient from the study if the adverse event was due to blood transfusion

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1:
Thanks for your advice on our paper. We have revised our paper according to your comments as follows:
1: exclusion criteria anemi. Many patients are slightly anemic. Is there a cut-off for the anemia? If any anemia is excluded then there might be a significant fallout of patients making the generalizability difficult.
According to the guidelines for blood transfusion in Europe and the United States, the highest trigger point for blood transfusion is HGB<9g/dl, so the range of anemia is defined as patients who may need transfusion treatment, and preoperative HGB<9g/dl. It has been clear that patients with 9g / dl may need blood transfusion, and preoperative intervention will affect the final outcome, so we think it is necessary to set the range.
Intraoperative blood transfusion requirements were also changed from 10g/dl to 9g/dl. （Page 10, line 31）
2: Long term anti-platelet therapy – please specify if low-dose acetyl salicylic acid counts as anti-platelet therapy.
3: You may need to specify what is meant with anti-coagulant and anti-platelet therapy - what medications does it include.
Comment 2 and 3 combine the answers: The expression of anticoagulant or antiplatelet therapy in the exclusion criteria has been improved and changed to a new expression—“Antiplatelet or anticoagulant therapy was administered at enrollment or discontinued for less than 7 days prior to study evaluation.”
Exclude all drugs that have anticoagulant or antiplatelet effects or that have been discontinued until the drug has been metabolized. So any anticoagulant or anti-platelet drugs include: such as aspirin, clopidogrel, agaltreban, heparin, low molecular weight heparin, warfarin, etc.
4: For clarification - all patients with a history of thrombosis will be excluded?
The specific definition of thrombotic events has been added to the revised draft—“Thrombotic events: Any blood clot in the vein or artery has been recorded before or at present.”
5: Page 13 – I don’t think that patients should be excluded due to hypotensive shock or other severe

intraoperative adverse event. It may be prudent to switch infusion/transfusion strategi accordingly in order to manage the situation according to best practice. However, I think it is important to keep the patient in the study follow-up. It is these situation that are important to know the outcome.
This stripper standard has been removed. Related adverse events may be due to blood transfusion, so follow-up should be continued to understand the final outcome.

References corresponding to the above responses are as follows:
1. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol. 2017;34(6):332-395. doi:10.1097/EJA.0000000000000630
2. Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA. 2016;316(19):2025-2035. doi:10.1001/jama.2016.9185
3. De Pietri L, Bianchini M, Montalti R, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. Hepatology. 2016;63(2):566-573. doi:10.1002/hep.28148

Response to Reviewer 2:
Thanks for your advice on our paper. We have revised our paper according to your comments as follows:
1: page 12 line 37: Total blood transfusion between 0 and 72 hours after surgery: Within 0-72 hours after the operation, patients will again receive a blood transfusion, including the total amount of RBCs, FFP and PLTs.
I'm sorry that there is something wrong with our statement. Let's change this sentence into: “Total blood transfusion in 0-72 hours after operation: If the patient needs a blood transfusion within 0-72 hours after the operation, we will record the total amount of RBCs, FFP and PLTs. If the patient does not receive a blood transfusion, the amount will be recorded as 0.” This does not mean that all patients will need transfusion within 72 hours of surgery, but it does mean that the actual volume of transfusion, which may be 0ml, may be 1000ml or more, is recorded.
2: Page 12 line 45: Patients who need a second operation due to postoperative bleeding within 72 hours will be excluded from this study. Why the exclusion of these patients.
The second operation for active bleeding within 72 hours will cause the outcome of the main study to be unmeasured, so we believe that this part of patients needs to be excluded, but it is recorded as an adverse event.
3：Page 13 line 5: If the condition progresses to severe intraoperative adverse events, such as shock, heart failure and massive blood loss, the patient will be excluded from the study. Again why exclude the patient from the study if the adverse event was due to blood transfusion.
This stripper standard has been removed. Indeed, this may be due to an adverse event due to transfusion and should be followed up to determine the outcome.

VERSION 2 – REVIEW

REVIEWER	Peter Cashin Uppsala University, Sweden
REVIEW RETURNED	07-Sep-2020

GENERAL COMMENTS	The authors have made relevant changes according to the prior review. They have answered the comments to satisfaction. No further comments have been forthcoming.