Response letter to reviewer's comments
World Journal of Transplantation

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Fan-Fang Ji
Science Editor

Re: Massive Haemorrhage in Liver Transplantation-Consequences , Prediction and Management (Ref No 00054036)

Dear Mr Ji,

We thank the reviewers for their helpful comments and suggestions. The authors have prepared responses to the reviewer comments on the above named manuscript. Please find below extracts from the manuscript that address the reviewers suggestions. The responses are highlighted in bold typeface. The new changes to the manuscript have been highlighted in the updated version uploaded to the submission website.

Comments

Reviewer 1

The paper deals with some aspects of "massive" bleeding prevention and management during liver transplantation.

Authors' aim was to focus on massive hemorrhage, as well as to report relevant lessons from other surgical specialties.

However in the main text, massive hemorrhage "sensu strictu" has only been generically defined, and relevant notes shortly reported in the paragraph Consequences of massive blood loss. For example, in the field of liver transplantation surgery speaking of Prediction of massive transfusion.. instead of prediction of transfusion, consequences of massive transfusion...instead of consequences of transfusion, risk factors for massive bleeding.. instead of risk factors for bleeding, etc explains only minimal difference in terms of studies explored, statements reported, citations, recommendations. Readers expect to have had these differences noticed after reading the title.

Liver transplantation surgery in contrast to trauma and obstetrics is largely an elective or semi-elective procedure where blood loss can be anticipated and a strategized around. Death from exsanguination, common in the early days of transplantation is now a rare event and therefore the traditional definitions of massive haemorrhage/transfusion are less at risk of survivor bias. Defining massive transfusion as 6 unit or more in 24 hours has been used in a number risk prediction studies for transfusion .[44–46]

Consequences of blood transfusion and massive transfusion better delineated in the following text :

Transfusion of red blood cells and blood products has been linked to adverse outcomes in OLT patients.[5657] Even modest transfusion requirements have been linked to prolonged lengths of hospital stay, with requirements of more than 6 units of red cells having the greater impact in decreased survival rates [37]. De Boer et al demonstrated a dose related effect in one year survival rates, with a hazard ratio of 1.37 per unit of platelets and 1.07 per unit of PRC, in their multivariate analysis of a cohort of 433 adult OLT patients[58]..

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Both short and long-term survival appears to be affected by intraoperative massive blood transfusion. Rana et al. found that an intraoperative blood transfusion of > 28 units was as significant risk factor for decreased 3 month survival in a study of 233 consecutive liver transplant recipients performed by the same experienced surgeon.[30] Intraoperative blood transfusion greater than 5 units was independently associated with reduced 3 and 5 years survival in a study of 102 Living donor liver transplant patients.[61]

The topic of coagulopathy, bleeding (massive or not), consequences and prevention, etc. has been already covered by many articles, reviews, and liver transplant-related literature (e.g Feltracco et al W J Hepatol 2013; Clevenger et al W J Gastroenterol 2014; Pandey et al W J Gastointest surg 2015, …..all not cited)

Selected suggested citations have been added to the manuscript;

Feltracco et al: see reference 31
Clevenger et al: see reference 34

The paragraph lessons from the battlefield delineates the recommended transfusion strategy for this setting; how can this teaching be transferred to the intraoperative phase of liver Tx procedure? As mentioned, coagulopathy of end stage liver disease is very different from the acquired coagulopathy of trauma, and bleeding mainly comes from portal hypertension. Authors have not properly linked these two situations. There is an accepted trend towards limiting Massive blood products transfusion; fluid restriction, fibrinogen, albumin, and "TEM" guided transfusion are now more appropriate.

Acute coagulopathy of trauma is characterised by ooze-type bleeding from mucosal regions, serosal surfaces and vascular access sites distinct from simple massive bleeding. [103] It consists of endogenous primary pathologies - disseminated intravascular coagulation (DIC) and acute coagulopathy trauma shock (ACOTS), and exogenous secondary pathologies that mimic DOC and ACOTS – hypothermia, acidosis, anaemia and dilutional coagulopathies. [104] Similarities between the pathophysiological changes that occur in liver transplantation have been suggested in a recent review on haemostasis in liver transplantation.[105] Derangements in thrombin-thrombomodulin-protein C system lead to anticoagulation in both trauma and liver transplantation patients. [105] Catecholamine release during traumatic injury is thought to directly damage the endothelium resulting in progressive de-endothelialisation. High levels of syndecan-1, a marker endothelial degradation is association with inflammation, coagulopathy and increased mortality in trauma patients, [106] and patients with end-stage liver disease have recently been demonstrated to have significantly higher levels than controls. [107] These levels are further elevated following graft reperfusion during liver transplantation.

Some paragraphs are more extensively written and some topics "more deeply" investigated with respect to others (e.g. preoperative risk factors for bleeding vs intraoperative factors)
The focus of our review is on prediction of massive transfusion. Most prediction literature uses pre-operative variables for prediction models. The paragraph 'intraoperative variables' refers mostly to surgical variables, therefore we have renamed 'surgical variables' to avoid confusion

Some words on : targeting a lower perioperative Hb levels (as a valuable strategy to reduce RBCs transfusion) .. deserve mentioning

There is significant variability among liver transplantation centres in methods of coagulation monitoring, transfusion triggers and transfusion protocols.[131] There is no evidence supporting specific haemoglobin or haematocrit triggers for packed RBC transfusion in OLT. However, data from other surgical and critical care populations indicates that transfusion

strategies targeting lower perioperative haemoglobin levels are safe and can lead to a reduction in RBC transfusion. A transfusion threshold of 70 g/lL for hemodynamically stable critically ill is suggested by data from the Transfusion Requirements in Critical Care (TRICC) trial. [132] The Transfusion Reduction Threshold Reduction Trial (TITRe2) compared the outcomes of a large population of cardiac surgical patients finding no evidence of harm with the use of a restrictive threshold of 75 g/L compared with a 'liberal' threshold of 90 g/L[133] . Similarly, results from a randomized surgical trials of hip surgery patients with pre-existing cardiovascular disease indicate that a restrictive RBC transfusion strategy is not associated with harm[134].. Some guidance can also be extrapolated from a randomize study performed in the setting of severe acute gastrointestinal bleeding excluding massive exsanguinating bleeding , concurrent acute coronary syndrome , stroke or peripheral vascular disease. All patients received endoscopic and treatment for bleeding within 6 hours if required. Patients were randomized to a 'liberal' RBC transfusion threshold of 90 g/L or 'restrictive' of 70 g/L. Thirty-one percent of patients in both groups had cirrhosis and bleeding was due to oesophageal varices in 21% of the patients. The authors observed improved mortality rates, reduced risk of further bleeding, and less complications such as pulmonary oedema, in patients randomised to the restrictive strategy .

Some statements not clear.. and "minor" errors: (e.g. first lines of Abstract, balanced..or rebalanced coagulopathy in liver cirrhosis?
Balanced changed to re-balanced in abstract

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Reviewer 2

The manuscript is an excellent and thorough review of biologic and clinical issues regarding massive blood loss and massive transfusion in liver transplantation.

I have only very minor comments or suggestions.

Page 5, 2nd paragraph: The last sentence ("The Prothrombin Time and International Normalized Ratio...") would be more comprehensible if split into 2 sentences.

The Prothrombin Time (PT) and International Normalised Ratio (INR) are useful markers of hepatic synthetic function. The INR is also used in combination with recipient age, bilirubin and creatinine is used to calculate the MELD score.

Page 10, last sentence: The assertion that "MTP's are likely not indicated" has not been rigorously studied, to my knowledge. A more neutral statement or a bit more theoretical explanation would be preferable.

While trials comparing fixed ratio-guided resuscitation with viscoelastic test-guided in liver transplantation are lacking it is usually a well-controlled procedure and most centres have access to point of care coagulation monitors to guide transfusion, the fixed ration MTP's are possibly only required in the most uncontrolled setting.

Once again thank you very much for the comments and opportunity to revise the manuscript

Yours sincerely

Stuart Cleland