May 16, 2018

Dear Editor,

Please find enclosed the reviewed manuscript in Word Format (file name: 38897-review.doc)

Title: PERIOPERATIVE THROMBOPROPHYLAXIS IN LIVER TRANSPLANT PATIENTS

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The manuscript has been improved according to the suggestions of reviewers:

1 Format and table 2 have been updated

2 Revision has been made according to the suggestions of the reviewer

RESPONSE OF AUTHORS TO REVIEWERS COMMENTS:

COMMENTS TO AUTHORS

Reviewer #00921744: Well written and comprehensive review on the hemostatic changes in patients with cirrhosis and consequences for thromboprophylactic therapy. I agree with the authors' conclusions and statements and have minor suggestions for further improvement:

1) Although the concept of rebalanced hemostasis is well explained, a reference to the original description of this theory is missing and could be included (Blood. 2010 Aug 12;116(6):878-85)

REPLY: We agree and we added the suggested reference in the introduction section.

2) In the abstract and on page 8 the authors mention the procoagulant changes in fibrin structure and platelet hyperreactivity. These prohemostatic features, however, do not appear in table 1, and I feel this should be harmonised.

REPLY: We appreciate your suggestion, we harmonised what required adding these prohemostatic features in table 1

3) I object to the reasoning that Child C patients have protein C levels similar to those found in patients with congentital protein C deficiency and therefore have a higher thrombotic risk. The thrombotic risk of the Child C cirrhosis is not and cannot be attributable to protein C deficiency only, or to a 'protein C/FVIII' imbalance. What matters is the net effect of all hemostatic changes (which is a normal to enhanced thrombin generating capacity), which is the resultant of all changes (including also decreases in antithrombin levels). Please rephrase.

REPLY: Thanks for the comment. It was not our intention to attribute only to protein C deficiency the potential thrombotic risk of Child C patients. We agree with you, the resultant of all changes in coagulation and anticoagulation factors that cause the thrombotic risk potential in cirrhotic patients. We have deleted the sentence

4) On page 10, it could also be mentioned that the observation that preoperative PVT increases the risk for post-operative HAT could indicate a role for hypercoagulability in post-transplant HAT (HPB (Oxford). 2016 Mar;18(3):279-86).

REPLY: Thank you for the suggestion. We added in the text a brief reference to this risk factor.

5) At the end of the section on viscoelastic tests it is mentioned that the sensitivity of TEG and ROTEM to the protein C pathway has not been studied - this is somewhat misleading. There are no protein C activators in relevant concentrations in whole blood, and therefore a clear limitation of VETs is absence of activation of the protein C pathway. This should be more clearly stated.

REPLY: Thanks for the comment, we modified the sentence from: "These devices are insensitive to the effects of vWF and factor XIII[50, 65, 66], their sensitivity to the protein C pathway has not been studied", to "These devices are insensitive to the effects of vWF and factor XIII[50, 65, 66], and they lack activation of the anticoagulant protein C system".

6) In the section on role of thromboprophylaxis it is stated that 'After LT, patients may be hypercoagulable because of an imbalance between coagulation and fibrinolytic mechanisms'. I think it has been established that after LT (and also after partial hepatectomy), patients are hypercoagulable because of enhanced thrombin generating capacity, despite prolongations in the PT (J Hepatol. 2010 Mar;52(3):355-61, Anaesthesia. 2016 Jun;71(6):657-68, Aliment Pharmacol Ther. 2015 Jan;41(2):189-98). I think it should also be more clearly stated that thromboprophylaxis should not be witheld on basis of post-operative prolonged PT values, as in reality coagulation is hyperactive.

REPLY: We agree. We added this explanation and the references in the text.

The added sentences in the section on role of thromboprophylaxis are: "It has been established as well that after LT and partial hepatectomy, patients are hypercoagulable because of enhanced thrombin generating capacity, despite prolongations in the PT[74-76]" and "In the light of the above mentioned observation thromboprophylaxis should not be withheld on basis of post-operative prolonged PT values, as in reality coagulation is

hyperactive and standard coagulation test are not truly representative of the real coagulation status in these patients".

7) In the section on low molecular weight heparin, the first sentence is inaccurate (LMWH inhibits FXa by enhancing antithrombin activity towards Xa). I don't undertstand the 'to a lesser extent, augments antithrombin III activity'.

REPLY: We are sorry, it should be a mistake. We delated the words "to a lesser extent"

COMMENTS TO AUTHORS

Reviewer#03311932: It is an interesting paper. Unfortunately, there is a lack of information regarding bibliography search methodology and for reviewers strategy of assignments. The paper can not be qualified even as a narrative review It is mandatory to include a properly described review methodology.

REPLY: Thanks for your suggestion. Following your right advice, I newly performed a systematic review describing the methodology of research and the selection criteria of the articles The new research has allowed to highlight an article more than those already mentioned in the work (Mori A, et al. Portal vein reconstruction in adult living donor liver transplantation for patients with portal vein thrombosis in single center experience. J Hepatobiliary Pancreat Sci 2015; 22(6): 467-474) and has suggested to eliminate an article which did not reflect the inclusion criteria (Nicolau-Raducu R, et al. Thromboprophylaxis With Heparin During Orthotopic Liver Transplantation: Comparison of Hepcon HMS Plus and Anti-Xa Assays for Low-Range Heparin. J Cardiothorac Vasc Anesth 2017). I described the new systematic review as follow:

A systematic literature search was performed independently by two of the authors (LDP and RM) using PubMed, and the Cochrane Library Central. The search was limited to humans and articles reported in the English language. No restriction was set regarding the type of publication, date or publication status. Participants of adult age and any sex who underwent living transplantation or living donor liver transplantation procedures were

considered. The search strategy was based on different combinations of words for each database. For the PubMed database, the following combination was used: *("liver transplantation" OR "liver transplant" OR "hepatic transplantation" OR "hepatic transplant") AND ("thromboprophylaxis" or "anticoagulation" or"antiplatelets" or "antithrombotic therapy" or "antithrombotic prophylaxis" or "prophylactic anticoagulation" or "anticoagulants" or "aspirin" or "heparin")*

The same key words were inserted in the search manager fields of the Cochrane Library Central. The search was broadened by extensive cross-checking of reference lists of all retrieved articles fulfilling inclusion criteria. For all databases, the last search was run on March 28, 2018.

Study Selection

The same two authors independently screened the title and abstract of the primary studies that were identified in the electronic search. The following inclusion criteria were set for inclusion in this systematic review: 1) studies reporting a thrombprophylactic therapy in liver transplant procedures; 2) studies reporting a description of the anticoagulation or antiplatelet therapy performed in liver transplant recipients; 3) if more than one study was reported by the same institute, only the most recent or the highest quality study was included.

The following exclusion criteria were set: 1) letters, comments and case reports; and 2) studies where it was impossible to retrieve or calculate data of interest.

Data Extraction

The same two authors extracted the following main data: 1) first author, year of publication and study type; 2) number and characteristics of patients; 3) effectiveness of the thromboprophylaxis performed in term of portal vein thrombosis, hepatic artery thrombosis, deep vein thrombosis and pulmonary embolism; 4) complications of thromboprophylaxis. Bias of the individual studies was categorized based on study design. All relevant texts, tables and figures were reviewed for data extraction. Discrepancies between the two reviewers were resolved by consensus discussion.

The results of the new systematic review performed are as follow:

The literature search yielded 634 articles; after the removal of all the articles that did not reflect the inclusion and exclusion criteria, a total of 11 articles [62, 77–80, 83-88] published between 1997 and 2018 were included in this systematic review. Three studies were prospective [77,78,85], only one was a prospective case control study [84] while all the others were retrospective [83, 61, 79] and four of these had control group [80, 86-88]; No papers reported multicentric data. All these studies included a total of 5192 patients (adult and children).

COMMENTS TO AUTHORS

Reviewer #02860895: This is a masterpiece review article, in which past reports concerning thromboprophylaxis in liver transplant were almost perfectly collected from comprehensive point of view and sufficiently assessed to be reconstructed as a firm doctrine. I can't raise any criticisms except for a few minor points, such as reuse of a technical term after definition of the abbreviation. Congratulations!

REPLY: Thanks for the comment. We replaced the technical terms with the proper abbreviations along the article.