Format for ANSWERING REVIEWERS

November 28, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6806-edited.doc).

Title: Left atrial thrombosis in an anticoagulated patient after bioprosthetic valve replacement: report of a case

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Name of Journal: *World Journal of Clinical Cases*

ESPS Manuscript NO: 6809

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

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

Reviewer 1:

Comment 1: "I would like to mention the following comment: It seems that the difference between this case and similar cases has not been clarified well. It would be better if the differences will emphasize more. Good Luck."

Reply: as recommended, we attempted to emphasize these differences on pages 6, as follows: "…On the other side, according with previous reports[Ref], we did not continue administering VKAs. Furthermore, we could not administer UFH or LMWH due to the history of immune thrombocytopenia, and moreover, we found some reports of LMWH-induced hepatotoxicity. Thus, we decided to administer fondaparinux. We found few evidence (two experimental models[Refs] and a case report[Ref]) supporting that the administration of fondaparinux (7.5 mg once per day) to prevent thrombosis in patients with mechanical heart valves. At that time, we speculated on the potential usefulness of a concomitant antiplatelet therapy (APT). However, we excluded this option considering that there was no evidence of improved efficacy and only an increased hemorrhagic risk.…". In addition, on page 7 we stated: "…Although VKA treatment represents the elective therapy in patients with left atrial thrombosis without mitral valve dysfunction, this case shows that it may be not suitable for avoiding thrombogenesis. This case shows that in very high thromboembolic risk patients VKA therapy never must be discontinued. This case also suggests that discontinuation of VKAs during the first three months after mitral valve surgery has to be carefully considered, especially in high thromboembolic risk patients.…".

Reviewer 2:

Comment 1: "This case report is carefully written and original, and only minor changes are recommended. 1. Highlight that a prothrombotic state may temporarily occur when anti-vitamin K are initiated or interrupted. 2. Elaborate on the relative safety and efficacy of novel oral anticoagulants in similar settings (eg dabigatran) 3. Discuss the potential usefulness of adjunct antiplatelet therapy on top of anticoagulation (eg with clopidogrel) to reduce the risk of thrombosis when warfarin is discontinued."

Reply: These remarks were included in the revised article as follows:

a) Page 5: "…The beginning of VKA therapy is burdened by a prothrombotic state, so we

associated LMWH for few days until reaching the INR target, as recommended by international guidelines to avoid thromboembolism....";

b) Page 5: "...There is no scientific evidence that the new oral antithrombotic agents (e.g. dabigatran, rivaroxaban and apixaban) are effective in these patients. Nevertheless, these drugs could represent a new interesting option because of their elevated safety and efficacy due to their pharmacodynamic profile and the absence of drug-to-drug interactions....".

c) Page 6: "...At that time, we speculated on the potential usefulness of a concomitant antiplatelet therapy (APT). However, we excluded this option considering that there was no evidence of improved efficacy and only an increased hemorrhagic risk...".

Reviewer 3:

Comment 1: The authors present a potentially interesting clinical note but the manuscript can be improved according to the following suggestions: 1. It would be helpful to mention that anticoagulation is mandatory to primary ischemic stroke prevention in a patient with a cardiac disorder because cardioembolic stroke is the subtype of ischemic infarct with the highest in-hospital mortality (around 20%) (Curr Cardiol Rev 2010; 6: 150-61.) 2. Authors must theorize on the possible etiology of the reversible liver disease the patient showed. 3. Authors must suggest the potential benefits of prescribing new oral anticoagulant (dabigatran, rivaroxaban or apixaban) in similar cases to the present one.

Reply: These remarks were included in the revised article as follows:

a) Page 5: "...This treatment strategy is mandatory for the primary prevention of cardioembolic ischemic stroke in patients with cardiac disorders (such as atrial fibrillation). Cardioembolic stroke is considered as an high-risk complication and it represents the subtype of ischemic infarct with the highest in-hospital mortality (20%)[Ref]....".

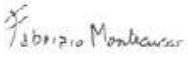
b) Page 6: "...First of all, we excluded the most frequent causes of acute liver disease. No evidence of viral hepatitis, cholelithiasis, neither use of hepatotoxic drugs nor toxins ingestion were found. Thus, we theorized that the cause of increased bilirubinemia and cholestatic index levels could be related to the right heart failure with blood hepatic stasis and secondary liver dysfunction....".

c) Page 7: "...Although VKA treatment represents the elective therapy in patients with left atrial thrombosis without mitral valve dysfunction, this case shows that it may be not suitable for avoiding thrombogenesis. This case shows that in very high thromboembolic risk patients VKA therapy never must be discontinued. This case also suggests that discontinuation of VKAs during the first three months after mitral valve surgery has to be carefully considered, especially in high thromboembolic risk patients. Although we used fondaparinux as an alternative strategy, the efficacy of this drug requires further validation in larger clinical trials. ...".

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Clinical Cases*

Sincerely yours,



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