Author's response to reviews

Title: Factors associated with excessive bleeding in cardiopulmonary bypass patients. A nested case-control study.

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Author's response to reviews: see over
Dear Editor:

We have changed some aspects from the original manuscript entitled “FACTORS ASSOCIATED WITH EXCESSIVE BLEEDING IN CARDIOPULMONARY BYPASS PATIENTS. A NESTED CASE-CONTROL STUDY”, following revisor’s suggestions. We hope that these changes make it more attractive for your journal.

Thanks for considering our manuscript.

Yours faithfully, Dr. Juan José Jiménez Rivera.

Revisor’s suggestions:

1. It is hard to understand how the distribution of PAI-1 genotypes in this group (absolute numbers not shown) can be of significance taking into account the number of patients included.

The distribution of PAI-1 polymorphism was 4G/G in 5 patients (19%), 4G/5G in 12 (46%), and 5G/G in 9 (35%), similar to that observed in 100 consecutive blood donors from our institution (4G/G: 21%; 4G/5G: 52%; 5G/G: 27%).

With respect to excessive postoperative bleeding according to PAI-1 polymorphism, we observed that 1 out of 5 (20%) 4G/G genotype, 5 out of 12 (42%) of 4G/5G genotype and 7 out of 9 (78%) 5G/G genotype showed excessive postoperative bleeding.

We agree with the reviewer that the series is not big enough to draw definitive conclusion. And even when neutral markers partially guarantee genetics associations, the relationship between 5G homozygosity of PAI-1 polymorphism and EB must be cautiously considered given the small sample size. However, these findings could be considered for future studies.

It has been included in the manuscript.

2. The reason for bleeding associated with the PAI-1 genotype is also not clear, since no efforts have been made to show whether systemic hyperfibrinolysis was more evident in 5G/5G genotypes than in the remainder.

The three genotypes of PAI-1 polymorphism showed significant differences in preoperative (Fig 2a) and 0h (Fig 2b) PAI-1 levels, ($P=0.046$ and $P=0.018$) respectively. Also, regarding coagulation we found the following results:
Variables | 5G/G (n=9) | 4G/5G (n=12) | 4G/G (n=5) | P  
--- | --- | --- | --- | ---  
Prothrombin Time (%) 0hr | 63 (53-71) | 74 (65-79) | 77 (75-83) | <0.01  
International normalized ratio 0hr | 1.66 (1.39-1.89) | 1.38 (1.33-1.46) | 1.37 (1.25-1.44) | 0.04  
Fibrinogen (mg/dl) 0hr | 230 (163-304) | 292 (262-432) | 357 (313-422) | <0.01  

3.- Discussion does not address correctly this aspect. Additional fibrinolytic tests such as D-dimer could be more informative regarding this point.

Regarding fibrinolysis, we did not find differences in t-PA levels between groups. However, EB patients showed lower levels of PAI-1 (P<0.01) and lower PAI-1/t-PA ratio (P=0.014) at 0 hours, with higher levels of D-dimer at 4 hours 1015 (944-1177) ng/mL vs 895 (753-905) ng/mL in the non-EB group (P=0.18)

It has been modified and included in the manuscript (Results and Discussion).

4.- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

We have excluded the original Figure 1 (distribution of PAI-1 polymorphism) and it has been added in the text. The actual figures 1 and 2 have the values in the Y axis.