



SDI Review Form 1.6

Journal Name:	International Blood Research & Reviews
Manuscript Number:	2013_IBRR_8146
Title of the Manuscript:	Effects of co-infusion of fresh frozen plasma and nafamostat mesilate on its clotting activities
Type of the Article	Original Research Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	1) Abstract: Please clarify aim of the study: no mention of influence of NM on whole blood 2) Abstract: Conclusion: second conclusion is a generalized statement and not based on results of the study: "might lead to obstruction of the plasma pheresis circuit when using NM as an anticoagulation" 3) There is a high frequency of heterozygous population with deficiency of protein C and protein S in the population as well as homozygous deficiency: however the incidence of spontaneous thrombosis in this population is very less: it is very conjectural statement to make that mere reduction of protein C and protein S activity secondary to NM leads to thrombosis: authors need to elaborate more in the discussion regarding the role of protein C and protein S deficiency and correlation with thrombosis 4) Authors need to discuss as to why NM and not GM (both being serine protease inhibitors) caused reduction in Protein C activity. They need to clearly mention that they have no rationale to justify reduction in Protein S activity by NM as it is not a serine protease enzyme. 5) Authors need to include additional data of baseline activity of "un-expired FFP" versus "expired FFP" regarding activity levels of	1) We changed from blood to whole blood in method and result of the abstract. 2) We changed the sentence in the conclusion of abstract. 3) The reviewer's comments are very suggestive. We are grateful for your comments. Therefore, we discussed the relationship between incidence of thrombosis in PC or PS deficient population and the blockade of plasmapheresis circuit when NM and FFP were used (167-170 in discussion). Prevalence of thrombophilia in the patients with PC deficiency, or PS deficiency is not extremely high [17]. Therefore, other episodes of pregnancy, infection, operation have been known to trigger the thrombophilia. However, we speculate that the decreased PS and PC activities by NM may induce the blockade the plasmapheresis circuit due to the contact with its blood foreign surface as a trigger. 4) The comment from reviewer is right. We changed the sentence in the discussion (148-149). 5) We showed data from unexpired FFP in the Table 1.



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	various coagulants and anti-coagulants including protein C and protein S or else give cross references for the same 6) Authors need to justify how NM caused significant increase in Anti-thrombin III activity when using whole blood from healthy volunteers 7) Table 4: statistical analysis is done based on comparison with of group treat with 5% dextrose solution: however no baseline values for the same are given: presume they have used information given in table 1. 8) Overall, not sure as to why the authors have included the role of NM on whole blood from human volunteers – it neither has correlation with the title; hypothesis or conclusion of the study; if that is the case: then authors need to justify differences and rationale of including whole blood and expired ffp for the study	6) We discussed the increased AT-III in the discussion section (150-155). AT-III activity in plasma from whole blood anticoagulated treated with NM for thirty minutes increased significantly compared to that with 5% glucose solution (Table 2), although co-infusion of FFP and NM did not affect AT-III activity (Table 1). The mechanism by which NM increased AT-III activity in the whole blood remains still unclear, because there are no papers about the relationship between AT-III activity in the whole blood and NM. However, NM has been reported to inhibit the leukocyte elastase release [16]. Therefore, we speculated that leukocyte-derived protease including elastase may break down the AT-III activity and NM may inhibit its action. We also added the reference 16 (246-247). 7) Another reviewer suggested that Table would be converted into Figure. Therefore, we decided that only Table 4 was converted into Figure. 8) Another reviewer also suggested that the title of our paper was not adequate. Therefore, we changed the title. Effects of co-infusion of plasma, whole blood and anticoagulants on its clotting activities
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<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments	Overall, the in vitro concept shown is good although the data analysis is from very limited tests (N=3) – however very difficult to make conjectural correlation with increased risk of thrombosis in clinical realm as reduction in protein c and protein s activity does not induce/ cause thrombosis in general population	Reviewr` comments are right. Therefore, we discussed it (167-170 in discussion). Prevalence of thrombophilia in the patients with PC deficiency, or PS deficiency is not extremely high [17]. Therefore, other episodes of pregnancy, infection, operation have been known to trigger the thrombophilia. However, we speculate that the decreased PS and PC activities by NM may induce the blockade the plasmapheresis circuit due to the contact with its blood foreign surface as a trigger.