Author's response to reviews

Title: Thromboembolic Risks of Recombinant Factor VIIa Use in Warfarin-Associated Intracranial Hemorrhage: a Case-Control Study.

Authors:

Sherry H-Y Chou (Schou1@partners.org)
Xuemei Cai (xcai@partners.org)
Rachael G Konigsberg (rachael.konigsberg@gmail.com)
Linda M Bresette (lbresette@partners.org)
Galen V Henderson (ghenderson@partners.org)
Farzaneh A Sorond (fsorond@partners.org)
Steven K Feske (sfeske@partners.org)

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Author's response to reviews: see over
Dear Dr. Rosengarten, Dear Reviewers,

Thank you very much for reviewing our manuscript and for your advice and comments. We have addressed comments of referee # 2 as per the editor’s directions, and we have modified the manuscript accordingly. Please see detailed point-by-point responses below. Thank you so much again for reviewing this work and considering for potential publication in BMC Neurology.

Referee # 2

Minor Essential Revisions
1. General comment: Pertinent p values should be included in the abstract as well as in the general body of the paper and not reserved for the tables. For example, in the abstract the authors state that “Clinically significant myocardial infarction (MI), defined as troponin > 1.0 ng/dL, occurred in 13% of rFVIIa-treated and 6% of standard therapy-treated patients,” but the difference has a p value of 0.52. Such an omission of the p value may lead casual readers to conclude that the rate of MI associated with rVIIa is twice that of conventional therapy. Another example, on page 9: I would definitely include p value (of 0.06) in the sentence “New EKG changes occurred in 42% of rFVIIa-treated cohort and 18% of standard therapy-wich cohort, with the predominant EKG changes being T-wave abnormalities,” as this strong trend might lead one to wonder if the difference in T-wave abnormalities would be statistically significant if the authors ran a separate analysis on T-wave changes alone. With regards to this difference, did the authors consider running a separate analysis?

We thank the reviewer for this very important comment, and have now included p-values in the abstract.
We did not run a separate analysis for the trend we noticed in T wave abnormalities, because this was not one of the two pre-specified end points of this study, and, given the small sample size, we want to minimize potential errors from multiple-testing. However, this is an important trend and we will follow this up with a future study.

2. Page 11 and Table 3: There was a high rate of surgical hematoma evacuation in the rVIIa group. In the early days of rVIIa use in wICH, there was a bias towards its use in those who were destined to go to the OR for clot evacuation. Do the records suggest such a bias in this cohort? Also, was there a correlation between surgical evacuation and death/withdrawal of care? The rates for each suggest that there might be.

We thank the reviewer for this very important observation. Overall, there is no significant correlation between surgical hematoma evacuation and death (p = 0.583). However, when we stratify the analysis by whether or not patients received FVIIa treatment, we noted that, while the group not treated by FVIIa showed no association between death and surgery, the FVIIa treated group had significantly better survival rate with surgical hematoma evacuation (53.6% vs. 82.4%, p = 0.044). We updated the manuscript to include this new result. This apparent higher survival in the surgical group in FVIIa-treated patients may suggest these patients derived more benefit from surgical hematoma evacuation compared to those who were not treated with FVIIa. However, given the retrospective nature of this study, we will not be able to prove this in the current study. We will certainly follow up with additional studies to further dissect this signal.

Discretionary Revisions
1. With the wider introduction of PCCs into the US market, the use of PCCs might be worth more of a discussion by the authors with regards to other (possibly safer) strategies for wICH treatment, given that the readership may not have great familiarity with the field of wICH therapies.

We have edited the manuscript accordingly to include a short discussion about PCC as an alternative reversal agent for wICH.

Thank you again for considering this manuscript.

Sincerely,

Xuemei Cai
Sherry H-Y Chou