Author’s response to reviews

Title: Post-operative re-bleeding in patients with hypertensive ICH is closely associated with the CT blend sign

Authors:

Guofeng Wu (wuguofeng3013@sina.com)
Zhengkui Shen (420339169@qq.com)
Likun Wang (769070308@qq.com)
Shujie Sun (sunshujie11@126.com)
Jinbiao Luo (ljbdoctor@126.com)
Yuanhong Mao (961766707@qq.com)

Version: 1 Date: 23 Apr 2017

Author’s response to reviews:

Reviewers` Comments and Responses

Dear editor

I have revised my manuscript in the light of the reviewers` comments point by point. The quality of the paper must have been improved. The revised parts of the text are marked as red. The English has been edited by the American Journal Experts and the Certificate is attached. The following contents are my responses. I hope this manuscript could be published in your journal.

Editor Comments:

✓ Please clarify in the abstract that all patients underwent surgery.

Responses-The abstract has been revised by adding the following sentences to the text. “All the patients underwent standard stereotactic MIS to remove the ICH within 24 hours following admission. There were 41 patients with a blend sign on initial CT and 85 patients without a blend sign on the initial CT.”
Please include in the discussion, that the type of surgical evacuation and its timing may play a role in the occurrence of re-bleedings; e.g. stereotactic aspiration only, i.e. without washing with saline, 4-5 days after ictus is not associated with significant re-bleeding.

Responses- Thank the editor for his or her comments. The postoperative re-bleeding might be associated with many factors, including surgical procedures, the time interval between the onset to the surgery, the abnormal coagulation mechanism, etc. In the present study, the MIS was followed by sterile saline washing. The effects of the coagulation mechanism abnormality and the time to surgery were ruled out. We have included the related factors in the discussions.

Reviewer reports:

Marc Alain Babi, MD (Reviewer 1): Interesting review of recurrent post-operative hemorrhage associated with the presence of the blend sign.

Overall, the authors describe the presence of a radiographic sign (blend sign) and its association with risk of rebleeding (ICH).

This article is worth publishing however will need extensive revision:

1. I recommend working on the verbiage. Several sentences are hard to follow or do not make sense at all

Responses-The manuscript has been edited by the American Journal Experts. The English should have been improved.

2. Please expend on the clinical significance of the blend sign (on the basis of previously published studies), rate of hematoma expansion (generally)

Responses- Thank the reviewer for his or her comments. In previously published studies, the hematoma expansion in patients with blend sign on initial CT was 24/29 with a rate of about 71%. In our study, the postoperative re-hemorrhage rate was 26.19% in total and 58.54% in 41 patients with the blend sign. We have discussed in the text of the Discussion section.

3. Hematoma expansion or growth carry the same meaning. Please use either terms.

Responses-We have removed the term hematoma expansion, just used the term: hematoma growth.
4. Expend on the limitation of this study.

Responses-We have revised the Discussion section by expanding the limitation of the present study.

Robbert-Jan van Hooff, M.D., Ph.D. (Reviewer 2): Hematoma expansion after intracerebral hemorrhage is a frequently encountered problem. As it is associated with poor clinical outcome, limiting the risk of hematoma expansion is key. Recently the novel blend sign has been introduced as a new imaging marker for the prediction of (spontaneous) hematoma growth. Authors aim to examine a possible relation between the presence of the blend sign and post-operative re-bleeding in a small population.

Although attempts have been made to reduce hematoma expansion in several clinical trials, all have failed to demonstrate improved outcome. In this light, the presented study is of interest. However, the manuscript could benefit from some improvements.

Introduction:

I would suggest to rephrase 'At present, there are no effective medical or surgical treatments for ICH, despite...'

Responses- Thank the reviewer for his or her comments. We were sorry for our inaccurate words. “at present…..” was taken directly from the literature. We have changed the sentence 'At present, there are no effective medical or surgical treatments for ICH, despite...' into the following one: “The ICH lacks an effective medical or surgical treatment despite the acknowledged pathophysiological benefits of achieved hemostasis and clot removal”

Methods:

- Informed consent was obtained only from the 'authorized representatives of the patients'. Was obtaining informed consent from participating patients directly in no case possible? If so, the reason(s) should be mentioned. Based on given GCS scores at least some patients should have been able to give informed consent.

Responses- Revised. Small number (35/126) of informed consents were obtained from both the authorized family member and the patients who have the ability to give the informed consent. We have revised the text.
Authors write that the presence of the blend sign was evaluated by two experienced reviewers. I'd suggest that the background/experience of these reviewers (neuroradiologist, neurosurgeon,...) is added.

Responses- Revised. The sentence has been changed into the following: Two experienced neuroimaging experts, who were blinded to the clinical information of the patients, acted as reviewers and independently evaluated the presence of the blend sign based on a recently proposed definition.

Patients receiving prior anticoagulant therapy were excluded from the study. What about the prior use of anti platelet drugs? Anti platelet drugs use prior to ICH might be associated with higher risks of post-operative bleeding.

Responses- Revised. All the patients received anticoagulant therapy and/or anti-platelet drugs prior to ICH were excluded from the study.

Authors define an intracranial re-hemorrhage as 'an increase in the hematoma volume of >33% compared to previous CT scan or the hyper-density appeared again in the focal region of the follow-up CT scan after it disappeared following surgery'. To which previous CT scan do authors refer? Was a control CT-scan systematically performed (immediately?) after surgery? And if so, what were hematoma volumes at this time point?

Responses- Thank the reviewer for his or her comments. We are sorry for our inaccurate words. “previous CT scan” referred the one before the postoperative follow-up CT scan which showed a possible hematoma growth. Generally, the postoperative follow-up CT scan was performed on the first day (the first postoperative CT) and the third day (the second postoperative CT) after surgery. Some patients needed a third or even a fourth postoperative CT follow-up.

Results:

- Assessing the inter observer reliability of a novel sign is indeed of importance for the value of this relatively new sign. Even though authors mention in the Methods section to have performed this analysis, no results of this analysis are given in the manuscript.

Responses- The results of the blend sign analysis has been added to the first part of the Results section.
✓ - Table 2 shows data of the post-operative re-hemorrhage vs. non re-hemorrhage group. Being n=33 and n=96 respectively, this would add up to a total 129 patients. However, based on Table 1 the sum of included patients would be 126 patients. This should be changed.

Responses-We are sorry for our carelessness. The data 96 in table2 has been revised.

✓ - Authors state that significant differences were found between the re-hemorrhage vs. non re-hemorrhage groups for the baseline hematoma volume, the GCS score and, most importantly because of the hypothesis, the presence of blend sign on initial CT scan. For the baseline hematoma volume and the GCS score p-values were of 0.045, for the presence of blend sign a p value of <0.001 is found. These values are more likely a reflection of the small study populations rather than a real statistical significant difference. I would recommend that these results should be interpreted with caution.

Responses- Thank the reviewer for his or her comments. The significance of the blend sign, the hematoma volume as well as the GCS score were just based on our small sample study. Large populations should be required to confirm our conclusions in the future study. The text has been revised in the light of the reviewer’s comments.

✓ - A positive predictive value of only 58.5% was found by authors. In my opinion, I would classify this to be low. Therefore, a comment on this should be mentioned in the Discussion section. Furthermore, the PPV is lower than the one found by Qi Li et al. (reference 9); could the authors give an explanation for this difference?

Responses- Thank the reviewer for his or her comments. We have mentioned the lower PPV in the discussion by adding the following words to the text: However, the positive predicative value of the blend sign for the post-operative re-haemorrhage was low, although the sensitivity was significantly higher than that found by Li Qi[1]. In Li’s study, the blend sign was used to predict the natural hemotoma growth which was very different from the post-operative re-hemorrhage after the minimally invasive surgery. This might be the reasons leading to the difference between the positive predictive value in our study and that reported in literature [1, 2]. The sample size might be another reason resulting in the difference in the positive predictive value between the two studies..

Discussion:

✓ - The time to baseline CT in both groups (i.e. blend sign positive and blend sign negative) is quite long. According to the authors, might this factor have been of influence on the results?
As hematoma expansion is most frequently seen in the first 6 hours after onset, the possible presence of the blend sign at 11/12 hours after onset, might be of limited value. Similarly, there are also indications to think that the frequency (and therefore importance) of the spot sign reduces over time.

Responses- Thank the reviewer for his or her comments. The time interval from the onset to the baseline CT was about 10 hours. Most hematoma growth occurred in the first hours in the literature. We were not able to rule out the possibility that the initial CT included some patients who had hematoma growth prior to baseline CT. The imaging marker spot sign, perhaps including the blend sign, reduce over time. We focused on the relationship between the blend sign and the postoperative re-bleeding. We were unable to pay more attention to the blend sign changes over time. The preoperative repeated CT did not show decreased number of the blend signs (only mild changes in the hematoma density). The time to baseline CT should not have influence on our results.

- The novel blend sign could be an interesting imaging marker to predict hematoma expansion after ICH. To my knowledge, this sign has until now only been evaluated in small cohorts. Why did authors prefer to examine this sign in a small cohort with an intervention, instead of a larger cohort without any surgical intervention?

Responses- Thank the reviewer for his or her comments. The blend sign has been just evaluated in a small population study (172 patients were included). A larger cohort should be required to examine this sign for predicting the hematoma growth in our future research. However, most of the patients admitted to our Emergency department received the minimally invasive surgery in the early stage if they are suitable for surgical intervention. We are expecting to find a imaging marker for predicting the postoperative re-bleeding. The ability to predict the postoperative re-haemorrhage after the minimally invasive surgery for ICH evacuation is of great clinical importance. So we preliminarily observed the value of the blend sign for predicting the postoperative re-bleeding.

- Aiming to avoid hematoma expansion after initial ICH is indeed key, obviously because of its negative influence on clinical outcome. To what extent was the presence of post-operative re-bleeding accompanied by clinical deterioration? As the mean post-operative volumes (3.56 vs. 3.40 ml) were quite small, I doubt that this was necessarily accompanied by clinical deterioration. It might therefore interesting to add clinical neurological parameters (i.e. NIHSS at 24 hours, etc.).

Responses- Thank the reviewer for his or her comments. We have revised the Results section by adding the postoperative re-hemorrhage volume to the text. On the third day after the procedures,
the average volume of the hematoma was 3.56±1.50 ml (with a clearance rate of 93%) in patients with blend sign and 3.40±1.65 ml (with a clearance rate of 92%) in the patients without the blend sign. The postoperative average ICH volume on the third day included all the 41 patients with the blend sign and the 85 patients without the blend sign. However, the average ICH volume after re-bleeding were 26.30±13.42 ml(from 12ml to 60ml) in all the 33 patients with postoperative re-hemorrhage revealed by a repeated CT follow-up. The postoperative re-hemorrhage volume was significantly increased compared to that on the previous postoperative CT follow-up.

Regretfully, we did not record the NIHSS in the early 24 hours following the surgery. We just obtained the NIHSS on the first week and the second week day. The NIHSS of the patients with postoperative re-hemorrhage on the second week was significantly higher than that of the patients without postoperative re-hemorrhage. The NIHSS on the second week was added to table2

- To which extent have authors ruled out the possibility that the possibly found correlation between prior blend sign and post-operative hemorrhage is for example not simply a reflection of the performed intervention? If I'm not mistaken all patients received a CT-scan prior to surgical intervention (performed at 24 hours). Was any hematoma expansion examined between initial CT and CT at 24 hours?

Responses- Thank the reviewer for his or her good comments. We were unable to ruled out the possibility that the postoperative re-hemorrhage was due to other factors such as emotion and blood pressure changes. This may be a limitation of the present study. All the patients received a repeated CT scan prior to surgery. Eight patients displayed hematoma growth on preoperative repeated CT. However, we focused on the relationship between the postoperative re-bleeding and the blend sign. So we were unable to analyze these data. We have added these data to the text of the Result section for reference.

- Authors conclude quite firmly that the CT blend sign could predict postoperative re-bleeding in patients with ICH that underwent MIS. Due to the very small groups (only 41 patients with positive blend sign on initial CT) and above mentioned comments authors should be careful in drawing conclusions. In general, I feel authors could elaborate more on the limitations of their presented study.

Responses- Thank the reviewer for his or her good comments. We have revised the discussions. The blend sign might be a possible indicator for predicting the postoperative re-bleeding. However, it should be confirmed by large cohort in the future study.