Author’s response to reviews

Title: Bleeding in patients who underwent scheduled second-look endoscopy 5 days after endoscopic submucosal dissection for gastric lesions

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Author’s response to reviews:

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Peter Laszlo Lakatos,
Section Editor,
BMC Gastroenterology
Manuscript ID BMGE-D-18-00011 entitled "Risk factors for bleeding in patients who underwent second-look endoscopy 5 days after endoscopic submucosal dissection for gastric lesions: a case control study"

Dear Prof. Lakatos,

We wish to resubmit our above-named manuscript to be considered for publication in BMC Gastroenterology. We have carefully considered all of the reviewer comments and addressed them as thoroughly as possible. Point-by-point responses to the reviewers’ comments are given below. We hope you will find our revised manuscript acceptable for publication in BMC Gastroenterology. Thank you for your consideration.

Sincerely yours,

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Point-by-Point Responses to the Editor’s and Reviewers’ Comments
Reviewer reports:

Francesca Galuppini, M.D. (Reviewer 1): This is a well-written manuscript about the risk of bleeding after second-look endoscopy (SLE) in the setting of gastric endoscopic submucosal dissection (ESD).

Although the work is well conducted and the main concerns are highlighted by the Authors, it does not have a great originality.

Response: We thank the reviewer for taking the time to review our manuscript.

Although previous randomized controlled studies revealed that second-look endoscopy (SLE) performed on the day following gastric endoscopic submucosal dissection (ESD) does not contribute to the prevention of bleeding after ESD in patients at low risk for bleeding, patients on antithrombotic drugs were excluded in those studies. Moreover, there is no article evaluating the incidence of post-ESD bleeding and status of post-ESD ulcer in patients who did not undergo SLE the day after of ESD. We scheduled SLE 5 days after ESD, when the recommencement of antithrombotic drugs can be expected to exhibit an effect, and investigated the risk of bleeding.

We have described this in the Background and Abstract sections, and also revised the Discussion section.

One of the concern I have is the following: How do the Authors argue the result that antithrombotic drugs affect more on later phase post-ESD bleeding?

Response: We have added the following sentences to the Discussion section to explain the increased effect of antithrombotic drugs on the later phase post-ESD bleeding.

“In this study, the incidence of post-ESD bleeding in the early and later phase were 2.3% and 2.8%, respectively, in the non-antithrombotic group, and 6.2% and 13.2%, respectively, in the antithrombotic group.”
“The present study also revealed that in the antithrombotic group, post-ESD bleeding occurred more frequently in the later phase than early phase (13.2% vs 6.2%). We speculated that bleeding is less likely to occur in the early phase because several days are required after resumption of the antithrombotic agents for the drug efficacy to reach a steady state [16-18]. Another possible reason is damage to the post-ESD ulcer during SLE, owing to hemostatic procedures and/or endoscopic examination itself.”

There are some typos and English could be reviewed.

Response: We have corrected the typographical errors before submitting the revised version of our manuscript.

Bhavana Bhagya Rao (Reviewer 2): This is a descriptive study of post ESD patient monitoring and attempts to identify factors predictive of bleeding. However it does have limitations as follows:

1. None of the included patients were on the newer anticoagulant agents, which are now increasingly in use.

Response: We thank the reviewer for taking the time to review our manuscript.

Owing to the retrospective nature of our study, none of the patients were on direct oral anticoagulants. We have mentioned this as a limitation, in the Discussion section of the manuscript.
2. In patients with early phase post-ESD bleeding was a diagnostic EGD performed at time of bleeding? If so what were the findings of this endoscopic eval and what sort of hemostasis was offered? Thereafter was a SLE also performed on Day 5?

Response: We performed a diagnostic EGD when patients exhibited early phase post-ESD bleeding. Scheduled SLE was not performed in these patients. We have added this information to the Results section of the manuscript.

We have also described the findings of the non-scheduled EGD performed for early phase post-ESD bleeding and the hemostatic procedure used, in the Results section.

3. Since antiplatelet and anticoagulant agents were restarted 2 days after procedure was SLE and the hemostatic procedures performed while on full anticoagulation on these patients?

Response: Yes. We have elaborated on this issue in the Methods section.

4. In the following statement in the results section "There was no statistically significant difference between the group of patients treated with antithrombotic agents and the group of patients not receiving treatment (p=0.237)" What is the parameter based on which the two groups are being compared here?

Response: We have revised this text as follows: “Among the 55 patients with high-risk ulcers, 18 (32.7%) were under antithrombotic treatment, while among the 234 patients with low-risk ulcers, 58 (24.8%) were receiving treatment. The difference in the prevalence of antithrombotic treatment between the two groups was not statistically significant (p=0.237) (Table 2).”
5. In this statement: "Univariate analysis of all 26 lesions with post-ESD bleeding revealed that a diameter of the resected specimen ≥40 mm (p=0.036) and antithrombotic treatment before undergoing ESD (p<0.001) were statistically significant factors for bleeding (Table 3)" please clarify if this is early or late phase post ESD bleeding.

Response: In this analysis, “post-ESD bleeding” includes both early phase post-ESD bleeding and later phase post-ESD bleeding. We have modified the sentence to clarify this issue.

6. The study is titled to be a case control study. However no controls have been identified.

Response: We apologize for the error. We have deleted the description “a case control study” from the title.

7. Further randomized controlled trials are needed to assess if SLE is necessary in post ESD patients and if prophylactic hemostasis is beneficial in patients with high risk ulcers. These questions are unanswered by current study.

Response: We have deleted the sentences from the manuscript as they appear vague and unsubstantiated in the present context.

8. The results do demonstrate that use of anti-thrombotic agents raises risk for post-ESD bleeding, but that is quite expected. The continued risk of bleeding despite prophylactic hemostasis, might also be related to the fact that antithrombotic therapy was ongoing during SLE and thereafter.
Response: As the reviewer mentioned, it is quite reasonable that anti-thrombotic agents increase the bleeding incidence. In this study, we scheduled SLE 5 days after ESD, when the resumption of antithrombotic agents was assumed to have achieved a steady effect, rather than 1 day after ESD. Bleeding incidence and the status of post-ESD ulcers have never been investigated in users and non-users of antithrombotic agents who do not undergo SLE a day after ESD. We believe that the data obtained in this study will serve as useful reference for future research, particularly for studies enrolling antithrombotic users.

9. Please give percentages and total 'n' in Table 2.

Response: We thank the editor for this valuable suggestion. We have added percentages and the absolute numbers in Table 2.