Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-21-3

Reviewer A

This is a retrospective single center study that evaluated the delayed post-polypectomy bleeding between patients who continued anticoagulants and those who discontinued those. No different incidence were found (3.2% vs 4.7%, p=0.76). The length of the anticoagulant withdrawal period did not affect the risk of bleeding. They concluded the continued use of anticoagulants might be acceptable for colorectal polypectomy.

I have some comments.

Major Comments

1. Please show clearly about study design, the inclusion criteria, and main outcomes in this study at methods section. It was difficult to understand such things. What is prospective design?

Reply 1: We wish to express our appreciation for the insightful comments on our paper. The inclusion and exclusion criteria were described in methods section (Page 6, line 11-16). The main outcome of our study was incidence of colorectal DPPB.

In this study, patients using anticoagulants and underwent colonoscopic polypectomy between January 2016 and September 2019 were retrospectively reviewed and analyzed. Besides, those who treated between October 2019 and September 2020 were prospectively compiled. We added the description in the methods section.

Changes in the text: Page 6 line 15-17, Page 7 line 6-9

2. Please clarify the definition of continue and discontinuation group. Because DOACs was recommended to withdraw before the procedure as you wrote, were those patients defined as discontinued group? Continued group included those who did not withdraw DOACs even in treatment day?

Reply 2: Yes, the definition of discontinuation group was those who interrupted anticoagulants before the colonoscopy including the day of procedure, and that of continuation group was those who without interruption and administered anticoagulants on the day of procedure.

Changes in the text: Page 9 line 8-10

3. Please show how many patients had DPPB in result section.

Reply 3: We added the number of patients and lesions experienced DPPB in result section.

Changes in the text: Page 10 line 20

4. How many patients would be required to prove equivalence or non-inferiority of two groups if you prospectively examine? Please describe such sample size and your limitation of this study in limitation.

Reply 4: Thanks for your helpful comment. According to our calculation, approximately 400

lesions in each group are required to prove equivalence and non-inferiority of two groups (at least 80 % power to show non-inferiority at a margin of 10 %). However, it was difficult to collect such number of sample size only in our institution. As you mentioned, we consider it as limitation of this study and added the description.
Changes in the text: Page 17 line 13-16

5. No other risks for DPPB was found in table 2? What do you think about that because several risk of DPPB was reported. Please describe about those in discussion compared with previous reports. Did it also depend on sample size?
Reply 5: In this study, some clinical factors related to patients and lesions were assessed for the risk of colorectal DPPB, and in the revised manuscript, we additionally analyzed the number of lesions resected per procedure reported as risk factor previously (18, 25). However, none of them were detected as significant risk factors (Table 2 and Table 4). As you mentioned, it may somewhat depend on our small sample size. However, another retrospective study comprising larger sample size of 788 lesions have demonstrated that there was no significant risk factor for colorectal DPPB other than anticoagulant use (11). Identifying the absolute risk factors for colorectal DPPB is difficult, and we consider that further studies to clarify them are required.
Changes in the text: Table 2, Table 4, and Page 17 line 18-21

6. Previous report showed HBT was higher risk of DPPB while your results did not. In addition, the rate of DPPB of each group was smaller than previous report. Were those influenced the proportion of DOACs? Please describe the difference about those in discussion. Moreover, DPPB of DOACs and warfarin was different?
Reply 6: In this study, the risk of DPPB was not significantly different between DOACs and warfarin (Table 2 and Table4). Although there was a tendency of higher DPPB rate in the continuation of warfarin group than that of DOACs, it was also not significantly different (9.5% [2/21] vs 1.4 % [1/72], respectively; P=0.127, Fig 2).

As you mentioned, HBT has been reported as risk factor for DPPB in previous studies (10-13), but our result was not. Furthermore, the incidence rate of DPPB of each group in our study was smaller than those of previous studies. We estimate there were some reasons for these discrepancies as follows.

1) The proportion of warfarin and DOACs.

In some of the previous studies, the proportion of warfarin users in HBT group was relatively higher than that of ours (approximately 70-90% vs 53.7%, respectively). In patients taking warfarin with HBT, both of warfarin and continuous intravenous infusion of unfractionated heparin (UFH) were restarted on the next day of colonoscopic polypectomy and continued until the PT-INR reached the therapeutic range. Consequently, a higher proportion of warfarin users with HBT led to a longer period of UFH infusion and could relate to a higher risk of DPPB.

2) Patients with concomitant use of antiplatelets were whether excluded or not.

In our study, patients receiving antiplatelet drugs were excluded to eliminate the impact of these drugs. However, previous studies have included the patients with concomitant use of antiplatelets and analyzed altogether. Consequently, it should additively affect the incidence of DPPB.

3) The incidence rate of DPPB was calculated based on number of either patients or lesions.

We calculate the incidence rate of DPPB based on the total number of lesions treated, whereas some studies calculated it based on that of patients. There is a controversy about the number of either patients or lesions should be used to calculate the incidence rate of DPPB. However, if calculated based on the number of patients, the incidence rate of DPPB would be higher owing to a lower denominator and the impact of HBT as risk factor would be emphasized. It can lead to bias and we consider that the assessment for the rate of colorectal DPPB would be better calculated based on the number of lesions to evaluate the risk of each lesion specifically.

Changes in the text: Page 14 line 18-Page 15 line 18

7. Takeuchi Y et al showed that DOACs with withdraw treatment day had DPPB even in cold polypectomy. And also the rate of DPPB in your group B was higher than others however it may not significant difference due to small sample size. Please describe those. (Takeuchi Y, et al. Ann Intern Med. 2019.)

Reply 7: Thanks for your insightful comment. Takeuchi Y et al. reported that the rate of DPPB in the group of patients with "continuous administration of anticoagulants with cold snare polypectomy" was 4.7 %, and that of group with heparin bridging and hot snare polypectomy was 12.0 % (16). Taking into account for the absence of heparin bridging in our group B, the rate of DPPB (8.8 %) might be reasonable.

Although it was not significantly different, the rate of DPPB in our group B was unexpectedly higher than that in our group C (3.2 %). As our impression, the rate of DPPB in our group C was lower than anticipated, but there are few studies investigating the incidence rate of colorectal DPPB with continuation of anticoagulants. Our result may not compromise the allowance of continuation of anticoagulants during the perioperative period of colorectal polypectomy, but we consider that further studies including a larger number of sample size to clarify the real value of colorectal DPPB rate with continuation of anticoagulants would be required.

Changes in the text: Page 14 line 3-5 and line 17-18

8. How do you think to evaluate DPPB using data of DOACs and warfarin? Because it may be potentially completely different DPPB rates between two drugs. The proportion may affect the results?

Reply 8: Some previous studies investigating the impact of anticoagulants on the risk of colorectal DPPB have analyzed the data of DOAC and warfarin users altogether (13, 16, 25-26). In addition, some of them performed subgroup analyses dividing patients into warfarin or DOAC users, as our study as well. In this study, there was no significant difference in the rate and risk of colorectal DPPB between DOAC and warfarin users (Fig 2, Table 2 and Table 4). We thus consider that the impact of the proportion of anticoagulants on our results was inconclusive.

Changes in the text: Page 16 line 11-14

9. You mentioned previous study had 0% DPPB in continued anticoagulants. But your results was not similar. And there were several papers about those terms. Please describe how much

incidence of DPPB in continued anticoagulants.
Reply 9: Friedland et al. described that the incidence rate of colorectal DPPB without interruption of anticoagulants in warfarin users was 0% (0/41) (24), and as you mentioned, that of our study was higher. On the other hand, Shimodate Y et al. reported that the rate of colorectal DPPB in the group with continuation of warfarin was 12.2% (5/41) (25), and the value was rather close to that of our study (the rate of DPPB in the continuation of warfarin group was 9.5 % [2/21], Fig 2). We added the description in discussion section.
Changes in the text: Page 16 line 11-13

10. Please describe the strength or merit of continued anticoagulants compared with discontinued those if their bleeding rate is similar. In addition, your reference 15 showed that discontinued anticoagulants had good results without thromboembolitic disease. Which do you think is better continued anticoagulants and discontinued anticoagulants without HBT? Please describe about those in discussion.
Reply 10: We consider that there are some merits of colonoscopic polypectomy with continued anticoagulants as follows. First, patients recommended not to interrupt anticoagulants by prescribing physicians (e.g., those who with high risk of thromboembolic diseases such as higher CHADS2 and CHA2DS2-VASc scores, and treated with cardiac valve replacement, etc.) become targets of performing colonoscopic polypectomy. Second, in cases of patients with difficulty in getting agreement of anticoagulant withdrawal (for reasons such as afraid of thromboembolic diseases, etc.), they can undergo treatment for colorectal lesions. Third, if patients fail to stop anticoagulants on the day of colonoscopy for some reasons and colorectal lesions eligible for colonoscopic polypectomy are detected, we can avoid to plan secondary colonoscopy on another day. Besides, if anticoagulant therapy was stopped and thromboembolic events unfortunately occurred during the peri-endoscopic period, it would be difficult to rule out the causal relationship between them. Therefore, we consider that if the bleeding rate is similar, colonoscopic polypectomy with continued anticoagulants is a better strategy than the management recommended in the present guidelines. We added the description in discussion section.
Changes in the text: Page 16 line 23-Page 17 line11

Reviewer B

The authors retrospectively compared delayed post-polypectomy bleeding (DPPB) rate in patients continued anticoagulants with patients discontinued anticoagulants. They concluded that continued use of anticoagulants during the peri-endoscopic period did not increase the DPPB rate and suggested that current JGES guideline recommendations for anticoagulant withdrawal before colonoscopic polypectomy may be reconsidered.

Strength: To compare the risk of colorectal DPPB among patients taking only anticoagulants (excluding patients taking antiplatelet agents)

Weekness:

1) Small sample size
2) Only univariate analysis for risk factor associated with DPPB

Although the manuscript are well written, I cannot accept the manuscript in the current form as the following reasons;

Major comments:
1) Patients taking either warfarin or direct oral anticoagulants (DOACs) were included in this study and the incidence of DPPB was compared continuation group with discontinuation group. However, warfarin is totally different from DOACs with regard to pharmacological mechanism. Hence, it is inadequate to evaluate DPPB in both patients taking warfarin and DOACs together.
Reply 1: We wish to express our appreciation to for the insightful comments on our paper. As you mentioned, there are differences of pharmacological mechanisms between warfarin and DOACs, and the assessment of the impact on colorectal DPPB would be better performed by each kind of anticoagulant drug class. However, it was difficult to perform such analyses because of our small sample size. We added it as limitation of this study in the discussion section.
Changes in the text: Page 18 line 5-11

2) Discontinuation group include both patients with presence and absence of heparin-bridging therapy (HBT). Because HBT has been previously reported as the risk for DPPB, it is better to divide discontinuation group into two groups, i.e. to compare the incidence of DPPB in the three groups (continuation group, non-HBT discontinuation group and HBT discontinuation group).
Reply 2: As you mentioned, HBT has been previously reported as risk for DPPB. In this study, we compared the incidence rate and risk of DPPB in the discontinuation group between with and without HBT (Table 3 and Table 4). However, the results of our study showed no significant difference in the incidence rate and risk of colorectal DPPB between them. The reasons for this discrepancy we estimated were described in discussion section, and replied in your comment 7.
Changes in the text: Page 14 line18-Page 15 line 18

3) Authors calculate the incidence of DPPB based on the total number of lesion treated (Page 7, line 2-3). The incidence of DPPB based on the total number of patients treated is correct. It is better to describe the number of resected polyps per patient in the patient's characteristics.
Reply 3: The number of lesions resected per patient was shown in Table 1 and 3, and we additionally assessed the risk for DPPB in Table 2 and 4.

There is considerable controversy about the number of either patients or lesions should be used to calculate the incidence of DPPB. In previous studies, the incidence of DPPB was calculated based on the total number of lesions (12, 20, 24, 27), but as you mentioned, some studies used the number of patients, besides others used that of both patients and lesions (5, 28).

Though our results showed no significance in univariate analyses, some characteristics related to lesion (e.g., size, location, and shape...) have been reported as risk factors for colorectal DPPB in previous studies. If incidence rate of DPPB was calculated based on the number of patients, it may be difficult to evaluate the risk of each lesion specifically. Thus, we

consider that the analysis of rate of colorectal DPPB would be better calculated based on the total number of lesions.
Changes in the text: Table 2 and Table 4, Page 15 line 9-18

4) Authors mentioned that this study was conducted retrospectively and had a partially prospective design (Page 7, line 3-4). Please describe design of this study more clearly. Which patient were prospectively treated?
Reply 4: In this study, patients using anticoagulants and underwent colonoscopic polypectomy between January 2016 and September 2019 were retrospectively reviewed and analyzed. Besides, patients treated between October 2019 and September 2020 were prospectively compiled. We added the description in the methods section.
Changes in the text: Page 7 line 6-9

5) Authors consulted the physician regarding the safety of discontinuation (Page8, line12-14). Please more clearly mention the criteria to decide management of anticoagulants.
Reply 5: In this study, in cases of patients expected to have high risk of thromboembolic diseases such as higher CHADS2 and CHA2DS2-VASc scores and those who treated with cardiac valve replacement, the physicians prescribing anticoagulants were not prone to recommend interruption of anticoagulants. Besides, as described in Page 9 line3-5, we explained all of the patients about the risk of hemorrhagic and thromboembolic events and the management of anticoagulants was determined individually. When patients requested to continue anticoagulants during the peri-endoscopic period (most of the reason was afraid of thromboembolic diseases), they were classified into the continuation group and underwent colonoscopic polypectomy with continuation of anticoagulants.
Changes in the text: Page 8 line 24-Page9 line 3

6) Patients in continuation group continued anticoagulants during perioperative period. Please mention timing of DOACs intake on the day of the procedure. Before or after the procedure? How long was the interval between DOACs intake and procedure?
Reply 6: JGES guidelines recommend that endoscopic mucosal biopsy and gastroenterological endoscopic procedures with low bleeding risk during DOAC treatment should be carried out at a time avoiding the peak DOAC blood concentration estimated from the time of administration (9). Hence, we instructed the patients in continuation group scheduled to perform colonoscopy in AM to administrate DOACs after the procedure, and those who scheduled colonoscopy in PM to administrate them in the morning. The interval between DOACs intake and procedure is estimated about 6-24 hours. We added the description in methods section.
Changes in the text: Page 9 line 15-18

7) In this study, the incidence of DPPB in both groups was relatively low (Page 10, line 8) comparing with the previous reports (e.g. Ref 24, Shimodate et al. Int J colorectal dis. 2019;34:1705-1712). Additionally, the incidence of DPPB in patients with HBT is quite low (Page 10, line 23-24). Please discuss the discrepancy comparing with previous reports.
Reply 7: As you mentioned, the incidence rate of colorectal DPPB in our study was relatively lower than that of above two studies, and that in patients with HBT, as well. We estimate the

reasons for this discrepancy were as follows.

1) The proportion of warfarin and DOACs.

In the above two studies, the proportion of warfarin users in HBT group was relatively higher than that of ours (approximately 70-90% vs 53.7%, respectively). In patients taking warfarin with HBT, both of warfarin and continuous intravenous infusion of unfractionated heparin (UFH) were restarted on the next day of colonoscopic polypectomy and continued until the PT-INR reached the therapeutic range. Consequently, a higher proportion of warfarin users with HBT led to a longer period of UFH infusion and could relate to a higher risk of DPPB.

2) Patients with concomitant use of antiplatelets were whether excluded or not.

In our study, patients receiving antiplatelet drugs were excluded to eliminate the impact of these drugs. However, in the above two studies, patients with concomitant use of antiplatelets were included and analyzed altogether. Consequently, it might additively affect the incidence of DPPB.

3) The incidence rate of DPPB was calculated based on the number of either patients or lesions.

We calculate the incidence rate of DPPB based on the total number of lesions treated, whereas the above two studies calculated it based on the total number patients. As we replied to your comment 3, there is a controversy about the number of either patients or lesions should be used to calculate the incidence rate of DPPB. However, if calculated based on the number of patients, the incidence rate of DPPB would be higher owing to a lower denominator, and a higher number of lesions per patients would be emphasized as a risk factor especially in studies comprised of patients with multiple lesions mainly (in fact, Shimodate et al. reported that higher number of lesions resected per procedure were risk factor for DPPB). We consider that assessment for rate of colorectal DPPB would be better calculated based on total number of lesions to evaluate the risk of each lesion specifically.

Changes in the text: Page 14 line 18-Page 15 line 18

8) Authors evaluated the rate of DPPB in the continuation group by each kind of anticoagulants in the Result section (Page 11, line 21-Page 12, line 2). As I mentioned in Major comment 1), it is better to compare the incidence of DPPB among each kind of DOACs, or omit the description.

Reply 8: As you mentioned in comment 1), there are differences in pharmacological mechanisms between warfarin and DOACs (and among DOACs, as well), and we agree that it would be better to compare the incidence and risk of DPPB by patients using each kind of anticoagulant drug. However, we could not perform such analysis because of our small sample size. We consider it as limitation of this study and added the description in discussion.

Changes in the text: Page 18 line 5-11

9) There are many tables in this manuscript. It is better to arrange the tables providing the essentials or transfer a few to the supplementary table.

Reply 9: Thanks for your helpful comment. In accordance to your suggestion, we changed Table 5 to Supplementary table 1.

Changes in the text: Page 12 line 2, Page 13 line 3 and 7, Table 5

Reviewer C

This study investigated the risk of delayed post-polypectomy bleeding after HSP and EMR for patients receiving anticoagulants. This is a well written study, however, this study has several limitations in the following areas.

1. Title is confusing. Recently, cold snare polypectomy (CSP) has spread rapidly. Therefore, I think that 'hot snare polypectomy and endoscopic mucosal resection' is better than 'polypectomy' in title and abstract.
Reply 1: Thanks for your helpful comment. Following your advice, we changed the description of "delayed post-polypectomy bleeding" to "delayed bleeding after hot snare polypectomy and endoscopic mucosal resection" in title and abstract.
Changes in the text: Page 1 line 1-2, Page 3 line 4-7, 9-10, 14, 17, 19, and 22-23

2. I think that EMR is not polypectomy. HSP and EMR are different procedures. Authors used the term of DPPB for delayed bleeding after EMR. It is strange.
Reply 2: As you mentioned, HSP and EMR are different procedures, though both of them are similar in resection techniques for colorectal polyps with electrocautery methods. EMR is defined as a treatment method with locally injection of fluids into the submucosa of superficial-type lesions, followed by snaring and resection (Tanaka S, et al. Dig Endosc. 2015; 27: 417-434.). By contrast, HSP is defined as a technique placing the snare over the lesion without submucosal injection and applying high-frequency current as the snare was closed (Kim HS, et al. Gastrointest Endosc. 2018; 87: 1539-1547.); this technique is mainly applied resection for pedunculated lesions in our institution. We added the description about above differences between them in methods section.
Changes in the text: Page 8 line 4-6

3. Why did authors exclude the patients receiving antiplatelets? Maybe, there were the patients receiving multiple antithrombotic agents. This is an important point in clinical practice.
Reply 3: In this study, we aimed to assess the impact of uninterrupted "anticoagulants" on the risk of colorectal DPPB. If antiplatelet drugs were concomitantly used, they may additively affect the bleeding risk and make it difficult to evaluate impact of anticoagulants only. To eliminate the impact of antiplatelets, we excluded the patients receiving these drugs.
Changes in the text: Page 10 line 15-16

4. More detail clinical information of colonoscopy is required. Did authors use the standard colonoscope? Or the magnifying colonoscope? If authors usually performed HSP or EMR at the time of the colonoscopy, it means that authors could not to use the magnifying scope in all cases. However, if authors did not remove the polyps in the first Colonoscopy, authors have been able to observe with magnifying scope in all cases. It is desirable that every polyp was examined in detail with the magnifying scope to determine the appropriateness of its resection using either EMR or HSP. It is important issue in clinical practice. In addition, Authors should add the description about the endoscopists (skill, number of experiences, ADR, etc).
Reply 4: Thanks for your thorough review. The colonoscopes used in our institution were

described in methods section (Page7, line 20-21). Among them, type CF-HQ290ZI, CF-HQ290I, and PCF-H290ZI are magnifying scope, and they can perform magnifying observation and resection of lesions in one procedure. As for PCF-Q260JI, it cannot perform magnifying observation, but endoscopic diagnoses were made by narrow band imaging and/or chromoendoscopy (using indigo carmine or crystal violet).

As our institutional characteristics, some trainees participated in this study and performed colonoscopy. However, most of procedures were performed by experienced endoscopists with performing more than 500 colonoscopies and none of our staff have ADR. The proportion of endoscopist with experience performing ≥500 colonoscopies were additionally described in Table 1 and Table 3, and the risk analysis for colorectal DPPB were shown in Table 2 and Table 4. As results, there were no significant differences.
Changes in the text: Page 7 line 1-2, line 18-19, line 21-23, and Table 1-4

5. Did authors perform HSP or EMR at the time of the first colonoscopy? If so, it means that authors discontinued the anticoagulants for all colonoscopies. If patients had not polyps, HSP or EMR were no needed. Did authors discontinue the anticoagulants for observation only?
Reply 5: As for the patients following the current JGES guidelines in our study (i.e., those who in the discontinuation group), we instructed them to stop administration of anticoagulants on the day of colonoscopy. However, if there were no colorectal lesions eligible for endoscopic resection and neither HSP nor EMR were performed (observation only), anticoagulants were resumed after the procedure on the day of colonoscopy. On the other hand, if either HSP or EMR were performed and DPPB was not suspected, anticoagulants were resumed on the next day after the colonoscopy as we described in methods section.
Changes in the text: Page 9 line 20

6. Authors described 'Resection methods, including HSP and EMR, were appropriately selected for each lesion by the treating physician' in the Methods section. I cannot agree this description. In Table 1, authors showed the lesion size. The mean of the lesion size in this study was about 7mm, and the rate of adenocarcinoma was 7.8%, 6.5%, 8.4%, respectively. The polyps more than 90% were benign (adenoma, hyperplastic polyp, SSA/P, inflammatory polyp, etc) and no needed HSP and/or EMR. Polyps less than 9mm and suspected benign with high confidence are not target for EMR. CSP is correct. I think that the adaptation of EMR is polyps of 10-20 (30) mm and with possibility of malignancy. The local injection for submucosal layer is performed for pathological diagnosis of vertical margin and evaluation the depth of submucosal layer. To perform EMR for polyps less than 9mm and suspected benign with high confidence is not correct. I think that the selects of endoscopic procedure of this study were not common. This is a fatal limitation of this study. Please explain in detail about the adaptation of endoscopic procedure for colorectal tumors in author's hospital. This is an important issue in clinical practice.
Reply 6: We appreciate the reviewer's pertinent comment. In our institution, resection of colorectal polyp with CSP was initiated to perform in 2016, and a substantial proportion of subcentimeter lesions were treated with HSP and EMR especially in the beginning of study period. As you mentioned, CSP is appropriate procedure to treat colorectal lesions less than 9mm with high confidence of benign nature, and we are now treating such lesions mainly with

CSP. We consider it as additional limitation of this study and described it in discussion section.
Changes in the text: Page 17 line 21-Page 18 line 5

7. The lesion size was small for EMR. There is the possibility that the lesion size effect the rate of DPPB. DPPB is the primary endpoint of this study, this is an important point in clinical practice.
Reply 7: As we replied to your comment 6, a substantial proportion of subcentimeter lesions especially in the beginning of study period were treated with HSP and EMR, and it would associate with relatively small lesion size in our study. However, in some previous studies from our country, the averages of lesion size were under 10 mm (10, 12-13, 16, 20, 26), and ours was not so far from them.

We agree that the bleeding risk of HSP and EMR would better to be evaluated for colorectal lesions larger than 10 mm or with highly suspicious of malignancy and described it as our additional study limitation.
Changes in the text: Page 17 line 24-Page 18 line 5

8. Authors described 'continued use of anticoagulants might be acceptable' in Discussion section and concluded 'the managements recommended in the present guidelines may be reconsidered' in the last sentence of the manuscript. I cannot agree this opinion. In this study, EMR performed for small polyps (maybe, including diminutive polyps too). The conclusion cannot be said from the results of this study.
Reply 8: As you mentioned, most of the lesions in our study were small for HSP and EMR, and we consider that further studies targeting colorectal lesions appropriate for those procedures (larger than 10 mm or with high suspicion of malignancy) are required to evaluate the risk of DPPB. We added the description in discussion section.
Changes in the text: Page 17 line 21-Page 18 line 5 and Page 18 line 14-15