Heparin bridge therapy and post-polypectomy bleeding

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AIM
To identify risk factors for post-polypectomy bleeding (PPB), focusing on antithrombotic agents.

METHODS
This was a case-control study based on medical records at a single center. PPB was defined as bleeding that occurred 6 h to 10 d after colonoscopic polypectomy and required endoscopic hemostasis. As risk factors for PPB, patient-related factors including anticoagulants, antiplatelets and heparin bridge therapy as well as polyp- and procedure-related factors were evaluated. All colonoscopic hot polypectomies, endoscopic mucosal resections and endoscopic submucosal dissections performed between January 2011 and December 2014 were reviewed.

RESULTS
PPB occurred in 29 (3.7%) of 788 polypectomies performed during the study period. Antiplatelet or anticoagulant agents were prescribed for 210 (26.6%) participants.
patients and were ceased before polypectomy except for aspirin and cilostazol in 19 cases. Bridging therapy using intravenous unfractionated heparin was adopted for 73 patients. The univariate analysis revealed that anticoagulants, heparin bridge, and anticoagulants plus heparin bridge were significantly associated with PPB ($P < 0.0001$) whereas antiplatelets and antiplatelets plus heparin were not. None of the other factors including age, gender, location, size, shape, number of resected polyps, prophylactic clipping and resection method were correlated with PPB. The multivariate analysis demonstrated that anticoagulants and anticoagulants plus heparin bridge therapy were significant risk factors for PPB ($P < 0.0001$). Of the 29 PPB cases, 4 required transfusions and none required surgery. A thromboembolic event occurred in a patient who took anticoagulant.

**CONCLUSION**
Patients taking anticoagulants have an increased risk of PPB, even if the anticoagulants are interrupted before polypectomy. Heparin-bridge therapy might be responsible for the increased PPB in patients taking anticoagulants.

**Key words:** Post-polypectomy bleeding; Heparin bridge therapy; Colonic polypectomy; Anticoagulants; Antiplatelets; Endoscopic surgery

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Core tip: Post-polypectomy bleeding (PPB) is the most common complication of colon polypectomy. In this study, we demonstrated that patients taking anticoagulants have an increased risk of PPB, even if the anticoagulants are interrupted before polypectomy. Heparin-bridge therapy might be responsible for the increased PPB in patients who take anticoagulants.

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**INTRODUCTION**
Colorectal cancer (CRC) is the third most common cancer and ranks fourth as a cause of death worldwide[1]. Endoscopic polypectomy is a safe and useful procedure to prevent CRC, reducing the CRC morbidity by 70%-80%[2,3]. Post-polypectomy bleeding (PPB) is the most common complication of endoscopic polypectomy with reported incidences ranging from 0.65% to 8.6%[4-6]. Risk factors for PPB include larger polyp size, right colon, pedunculated type and anticoagulants[6-9], although these are still controversial. Major guidelines recommend cessation of anticoagulants before polypectomy and heparin bridge therapy for high thrombotic risk cases[10-12]. Nevertheless, a study demonstrated that the incidence of PPB was higher in patients taking anticoagulants, even if they were interrupted[13]. Recently, another study suggested that heparin bridge therapy might be associated with a higher PPB rate in patients taking anticoagulants[14]. Studies, including a meta-analysis, suggest that bridging therapy might be associated with high bleeding risk after invasive procedures including polypectomy in patients taking anticoagulants[15,16]. A randomized double-blind placebo-controlled trial demonstrated that bleeding risk was higher in patients taking bridging therapy than in those without bridging and that thromboembolic risk was similar in both groups[17]. The aim of this study was to elucidate the risk factors for PPB including antithrombotic agents and heparin bridge therapy.

**MATERIALS AND METHODS**
This is a case-control study based on medical records at Sapporo Medical University Hospital. All colonoscopic polypectomies, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) performed between January 2011 and December 2014 were included. Patient-, polyp- and procedure-related factors were obtained from the database. The patient-related factors included age, gender, comorbidity, antithrombotic agents (antiplatelet and anticoagulant). The polyp-related factors included location (right colon: cecum, ascending colon, and transverse colon; left colon: descending colon, sigmoid colon, and rectum), size, shape and number of resected polyp. The procedure-related factors were prophylactic clipping and resection method (polypectomy, EMR or ESD). PPB was defined as bleeding that occurred 6 h to 10 d after colonoscopic polypectomy and required endoscopic hemostasis. For such cases, a second-look colonoscopy was performed to identify the origin of the bleeding and endoscopic hemostasis was performed immediately.

The management of antithrombotic agents was based on the Japanese Gastroenterological Endoscopy Society guidelines published in 2005[18]. All anticoagulants and antiplatelets were ceased before polypectomy except in high thrombotic risk cases. Aspirin and thienopyridines (ticlopidine and clopidogrel) were stopped 5-7 d before polypectomy and other antiplatelets such as cilostazol, dipyridamole or beraprost were ceased 24 to 48 h before the procedure. The anticoagulants used during the study period were warfarin, dabigatran and rivaroxaban. Warfarin was ceased 4-5 d before polypectomy and dabigatran and rivaroxaban were stopped 24 to 48 h prior to the procedure. All antiplatelets and anticoagulants were resumed 24 to 48 h from polypectomy. For high
thrombotic risk patients, intravenous unfractionated heparin (UFH) was administered after ceasing anti-coagulants or antiplatelets. UFH was started 2-3 d before polypectomy at 10000 to 15000 U/d, which was adjusted by monitoring APTT. The UFH was stopped 4-6 h prior to polypectomy and resumed 2-6 h after the procedure.

The instrument used for polypectomy and EMR was a SnareMaster (Olympus medical, Tokyo, Japan) and normal saline was injected for EMR. The instruments used for ESD were a Hook knife (Olympus medical, Tokyo, Japan) or Flush Knife BT (Fujifilm, Tokyo, Japan). Glycine (Chugai Pharmaceutical Co., Ltd.) and hyaluronic acid was used for submucosal injection in ESD. An electrosurgical unit (VIO 300D; ERBE, Tubingen, Germany) was set according to the manufacturer’s instructions and a mixed current was used for resection. As cold polypectomy was not adopted during the study period, all the procedures including polypectomy, EMR and ESD were performed using electrocautery (hot). PPB was treated endoscopically using soft coagulation, hemocliping, or epinephrine injection.

Student’s t-test was used for continuous variables and chi-square test or Fisher’s exact test was used for categorical variables. First, a univariate analysis was performed for all possible risk factors. The significant variables were taken as potential risk factors and were included in the multivariate logistic regression model. All P values were two-sided and the results were considered significant when P values were < 0.05.

**RESULTS**

A total of 788 patients underwent polypectomy during the study period. Antithrombotic agents were prescribed to 210 (26.6%) patients; antiplatelets to 83 (10.5%), antiplatelets to 154 (19.5%), both to 28 (3.6%), dual antiplatelet agents to 59 (7.5%) and triple antiplatelet agents to 8 (1.0%) patients. Bridging therapy using intravenous UFH was adopted for 73 patients (9.3%) (Table 1). All antiocoagulants and antiplatelets were ceased before polypectomy except for aspirin or cilostazol in 19 cases. PPB occurred in 29 (3.7%) of 788 polypectomies performed. Four PPB patients required transfusion and none required surgery. None of the following were correlated with PPB: age, gender, polyp location, polyp size, polyp shape (flat vs sessile vs pedunculated), number of polyps resected, prophylactic clipping, resection method (polypectomy or EMR vs ESD), antiplatelets and antiplatelet plus heparin bridge therapy (Table 2). Anticoagulants, heparin bridge therapy, and anticoagulants plus heparin bridge therapy (meaning that anticoagulants were substituted by heparin before polypectomy) were significantly associated with PPB (Table 2).

The multivariate logistic regression analysis revealed that anticoagulants and anticoagulants plus heparin bridge therapy were independent risk factors for PPB whereas heparin bridge therapy alone was not (Table 3). The odds ratios of anticoagulants and anticoagulants
plus heparin were 4.2 (95% CI: 1.126-15.87, \( P = 0.033 \)) and 9.8 (95% CI: 3.771-25.443, \( P < 0.001 \)), respectively.

Eleven PPB cases that took anticoagulants are summarized in Table 4. Seven patients had atrial fibrillation, seven had valvular heart disease and one had cerebrovascular disease. Warfarin, dabigatran and antiplatelets were prescribed to 9, 2 and 3 patients, respectively. Anticoagulants and antiplatelets were ceased before polypectomy in all cases and heparin bridge therapy was carried out for 10 of 11 patients. Bleeding occurred 1 to 6 d after polypectomy. All PPB were successfully treated by endoscopy but re-bleeding occurred in 3 cases. Seven patients resumed anticoagulants before PPB but the PT-INR at PPB were within therapeutic range. Eight patients were still on heparin at PPB and APTT at PPB were elevated in 2 patients. A thromboembolic event occurred in a patient after ceasing anticoagulant treatment.

### DISCUSSION

Our study demonstrated that anticoagulants and anticoagulants plus heparin bridge therapy might be independent risk factors for PPB despite periprocedural interruption. Several studies demonstrated a close correlation between PPB and anticoagulants\(^{[5,13,14,19-21]}\). Sawhney et al\(^{[6]}\) demonstrated that resuming anticoagulants following polypectomy was strongly associated with severe delayed PPB. Witt et al\(^{[7]}\) also suggested the incidence of PPB was higher in patients receiving anticoagulation therapy, even though warfarin was interrupted for the procedure.

It has been recently suggested that heparin bridge therapy might be associated with PPB after ceasing antithrombotic agents\(^{[15]}\). Inoue et al\(^{[14]}\) demonstrated that the incidence of PPB was significantly higher in a heparin bridge group than in a non-heparin bridge group (20.0% vs 1.4%, respectively). Ishigami et al\(^{[20]}\) also demonstrated that heparin-bridging therapy is associated with a high risk of PPB regardless of polyp size.

A meta-analysis\(^{[15]}\) and large-scale studies\(^{[16,17]}\) also suggest that heparin bridge therapy might increase bleeding after invasive procedures including polypectomy in patients taking anticoagulants. Notably, a randomized double-blind placebo-controlled trial demonstrated that the incidence of major bleeding was higher in a bridging group than in a no-bridging group whereas the incidence of arterial thromboembolism was similar in both groups (the BRIDGE trial\(^{[17]}\)).

Our study also demonstrated that anticoagulants and anticoagulants plus heparin-bridge therapy were independent risk factors for PPB. Anticoagulants were interrupted in all cases and PT-INR at PPB was below the therapeutic range in most cases. Of 11 PPB cases using anticoagulants, 10 underwent heparin bridge therapy and 8 were on heparin at the time of PPB. Heparin bridge therapy might be responsible for PPB in patients taking anticoagulants, though APTT at PPB was elevated in only 2 cases. Heparin might have a synergic effect with anticoagulants, which is not measurable using APTT or PT-INR.

Interestingly, antiplatelets plus heparin was not associated with PPB in our study. Previous studies demonstrated that aspirin is not a risk factor for PPB in conventional polypectomy\(^{[19,20,23-25]}\). Yousfi et al\(^{[23]}\) demonstrated that there was no statistically relevant difference in prior aspirin use before polypectomy in a bleeding group and matched controls. Manocha et al\(^{[24]}\) demonstrated PPB rates of patients on aspirin and NSAIDs vs those not on aspirin or NSAIDs (3.2% vs 3.0%). In contrast, polypectomy on clopidogrel is likely to have increased risk for PPB\(^{[24]}\). It might be prudent to postpone polypectomy for high thrombotic risk patients taking clopidogrel.

These results might reflect the mechanism of hemostasis: anticoagulants work on the secondary hemostasis process such as manufacturing of fibrin, while antiplatelet agents work on the primary hemostasis such as the cohesion of platelets. As the secondary hemostasis is stronger than the primary, anticoagulants including heparin might cause PPB more frequently than antiplatelets\(^{[21]}\).
The present study had several limitations. First, this study was a retrospective study conducted at a single institution. The second limitation was the small sample size. As PPB is a rare complication with incidences ranging from 0.65% to 8.6%[6-6], the small sample size of our study might have led to the ambiguous conclusion. Despite these limitations, we believe that the results of this study may have important implications for clinical practice. A further study on a larger scale will be needed.

In conclusion, patients taking anticoagulants have an increased risk of PPB, even if anticoagulants are interrupted before polypectomy. Heparin-bridge therapy might be responsible for the increased PPB in patients taking anticoagulants. A prospective study to compare bridging with no bridging at polypectomy is warranted.

COMMENTS

Background
Post-polypectomy bleeding (PPB) is the most common adverse event of colonoscopic polypectomy. Past studies demonstrated risk factors for PPB but it is still controversial whether anti-thrombotic agents are associated with PPB. Major guidelines recommend ceasing anticoagulants before polypectomy and substituting by heparin (heparin-bridge) in high thrombotic risk cases.

Research frontiers
Recent studies suggest that heparin-bridge might increase bleeding after invasive procedure including polypectomy.

Innovations and breakthroughs
This study demonstrated that PPB increased in patients taking anticoagulants, despite they were ceased before polypectomy according to the guidelines. From the study results, the authors speculated that heparin-bridge might be responsible for PPB in patients taking anticoagulants.

Applications
When ceasing anticoagulants before polypectomy, no bridging might be better than heparin-bridge to reduce PPB. Prospective study is necessary to compare incidence of PPB as well as thrombotic events between 2 groups with and without heparin-bridge.

Terminology
In this study, PPB was defined as bleeding that occurred 6 h to 10 d after polypectomy and required endoscopic hemostasis.

Peer-review
The authors showed that the PPB was associated with heparin bridging therapy. Patients who took antiplatelets during heparin bridging therapy showed the high incidence of PPB. This study is new evidence about PPB.

REFERENCES
1 Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, Machtney MF, Allen C, Hansen G, Woodbrook R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, Te Ao B, McMahon B, Karimkhanı C, Yu C, Cooke GS, Schwebel DC, Carpenter DO, Pereira DM, Nasr D, Kazi DS, De Leo D, Plass MG, Younis M, Yonemoto N, Breitborde Y, Yip P, Pourmalek F, Lotufo PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, DellaValle R, Weintrob R, Lucas R, Hay R, Rojas-Rueda D, Westerman R, Sepanlou SG, Nolte S, Patten S, Weinchenthal S, Ahera SF, Fereshtehnejad SM, Shiae I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov VV, Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshrami B, Williams HC, Shibuya K, Dandona R, Murthy K, Cowie B, Amare AT, Antonio CA, Castañeda-Ojuela C, van Goor CH, Violante F, Oh IH, Derbik E, Soreide K, Knibbs L, Kereselidze M, Green M, Cardenas R, Roy N, Tillmann S, Li Y, Krueger H, Monalsta L, Dey S, Sheikhbahaei S, Hafizi-Nejad N, Kumar GA, Seereamarody CT, Dandona L, Wang H, Vollset SE, Mokdad A, Salomon JA, Lozano R, Vos T, Forouzanfar M, Lopez A, Murray C, Naghavi M. The Global Burden of Cancer 2013. JAMA Oncol 2015; 1: 505-527 [PMID: 26181261 DOI: 10.1001/jamaoncol.2015.0735]
2 Webb WA, McDaniel L, Jones L. Experience with 1000 colonoscopic polypectomies. Ann Surg 1985; 201: 626-632 [PMID: 3873221]
3 Rosen L, Bus DS, Reed JF, Nastasea SA. Hemorrhage following colonoscopic polypectomy. Dis Colon Rectum 1993; 36: 1126-1131 [PMID: 8253009]
4 Heldwein W, Dollhopf M, Rösch T, Meinig A, Schmidtsdorff G, Hasford J, Hermanek P, Burlereinger R, Birkner B, Schmitt W. The Munich Polypectomy Study (MUPS): prospective analysis of complications and risk factors in 4000 colonic snare polypectomies. Endoscopy 2005; 37: 1116-1122 [PMID: 16281142 DOI: 10.1055/s-2005-870512]
5 Sawhney MS, Salfiti N, Nelson DB, Lederle FA, Bond JH. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy 2008; 40: 115-119 [PMID: 18253906 DOI: 10.1055/s-2007-966959]
6 Rutter MD, Nickerson C, Rees CJ, Patrick J, Blanks RG. Risk factors for adverse events related to polypectomy in the English Bowel Cancer Screening Programme. Endoscopy 2014; 46: 90-97 [PMID: 24477363 DOI: 10.1055/s-0033-1344987]
7 Kim JH, Lee HJ, Ahn JW, Cheung DY, Kim JI, Park SH, Kim JY. Risk factors for delayed post-polypectomy hemorrhage: a case-control study. J Gastroenterol Hepatol 2013; 28: 645-649 [PMID: 23369027 DOI: 10.1111/j.1440-1746.2012.06884.x]
8 Gandhi S, Narula N, Mosleh W, Marshall JK, Farkouh M. Meta-analysis: colonoscopic post-polypectomy bleeding in patients on continued clopidogrel therapy. Aliment Pharmacol Ther 2013; 37: 947-952 [PMID: 23530880 DOI: 10.1111/apt.12292]
9 Wu XR, Church JM, Jarrar A, Liang J, Kalady MF. Risk factors for delayed postpolypectomy bleeding: how to minimize your patients’ risk. Int J Colorectal Dis 2013; 28: 1127-1134 [PMID: 23440363 DOI: 10.1007/s00384-013-1661-5]
10 Acosta RD, Abraham NS, Chandrasekharva H, Chathadi KV, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fisher DA, Fonkalsrud EW, Delate T, McCool KH, Dowd MB, Clark NP. Crowther
MA, Garcia DA, Ageno W, Dentali F, Hylek EM, Rector WG. Incidence and predictors of bleeding or thrombosis after polypectomy in patients receiving and not receiving anticoagulation therapy. *J Thromb Haemost* 2009; 7: 1982-1989 [PMID: 19719825 DOI: 10.1111/j.1538-7836.2009.03598.x]

14 Inoue T, Nishida T, Maekawa A, Tsujii Y, Akasaka T, Kato M, Hayashi Y, Yamamoto S, Kondo J, Yamada T, Shinzaki S, Iijima H, Tsujii M, Takehara T. Clinical features of post-polypectomy bleeding associated with heparin bridge therapy. *Dig Endosc* 2014; 26: 243-249 [PMID: 23730922 DOI: 10.1111/den.12123]

15 Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation* 2012; 126: 1630-1639 [PMID: 22912386 DOI: 10.1161/CIRCULATIONAHA.112.105221]

16 Steinberg BA, Peterson ED, Kim S, Thomas L, Gersh BJ, Fonarow GC, Kowey PR, Mahaffey KW, Sherwood MW, Chang P, Piccini JP, Ansell J. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation* 2015; 131: 488-494 [PMID: 25499873 DOI: 10.1161/CIRCULATIONAHA.114.011777]

17 Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA, Jacobson A, Jaffer AK, Kong DF, Schulman S, Turpie AG, Hasselblad V, Ortel TL. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med* 2015; 373: 823-833 [PMID: 26095867 DOI: 10.1056/NEJMoa1501035]

18 Ogoshi K, Kaneko E, Tada M, Mine T, Yoshino J, Yahagi N, Goto S. The management of anticoagulation and antiplatelet therapy for endoscopic procedures. *Gastroenterol Endosc* 2005; 47: 2691-2695

19 Kim HS, Kim TI, Kim WH, Kim YH, Kim HJ, Yang SK, Myung SJ, Byeon JS, Lee MS, Chung IK, Jung SA, Jeen YT, Choi JH, Choi KY, Choi H, Han DS, Song JS. Risk factors for immediate postpolypectomy bleeding of the colon: a multicenter study. *Am J Gastroenterol* 2006; 101: 1333-1341 [PMID: 16771958 DOI: 10.1111/j.1572-0241.2006.00638.x]

20 Hui AJ, Wong RM, Ching JY, Hung LC, Chung SC, Sung JJ. Risk of colonoscopic polypectomy bleeding with anticoagulants and antiplatelet agents: analysis of 1657 cases. *Gastrointest Endosc* 2004; 59: 44-48 [PMID: 14722546 DOI: 10.1016/S0016-5107(03)02307-1]

21 Beppu K, Osada T, Sakamoto N, Shibuya T, Matsumoto K, Nagalaara A, Terai T, Ogihara T, Watanabe S. Optimal timing for resuming antithrombotic agents and risk factors for delayed bleeding after endoscopic resection of colorectal tumors. *Gastroenterol Res Pract* 2014; 2014: 825179 [PMID: 25548556 DOI: 10.1155/2014/825179]

22 Ishigami H, Arai M, Matsumura T, Maruoka D, Minemura S, Okimoto K, Kasamatsu S, Saito K, Nakagawa T, Katsuno T, Yokosuka O. Heparin-bridging therapy is associated with a high risk of post-polypectomy bleeding regardless of polyp size. *Dig Endosc* 2016; Epub ahead of print [PMID: 27368065 DOI: 10.1111/den.12692]

23 Youssf M, Gostout CJ, Baron TH, Hernandez JL, Keate R, Fleischer DE, Sorbi D. Postpolypectomy lower gastrointestinal bleeding: potential role of aspirin. *Am J Gastroenterol* 2004; 99: 1785-1789 [PMID: 15330919 DOI: 10.1111/j.1572-0241.2004.30368.x]

24 Hopper AD, Bourke MJ, Williams SJ, Swan MP. Giant laterally spreading tumors of the papilla: endoscopic features, resection technique, and outcome (with videos). *Gastrointest Endosc* 2010; 71: 967-975 [PMID: 20226451 DOI: 10.1016/j.gie.2009.11.021]

25 Manocha D, Singh M, Mehta N, Murthy UK. Bleeding risk after invasive procedures in aspirin/NSAID users: polypcetomy study in veterans. *Am J Med* 2012; 125: 1222-1227 [PMID: 23164486 DOI: 10.1016/j.amjmed.2012.05.030]

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