

Retrospective Study

Heparin bridge therapy and post-polypectomy bleeding

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Abstract**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%)

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

Table 1 Prescription of antithrombotic agents

Anticoagulants	<i>n</i>
Warfarin	68
Dabigatran	12
Rivaroxaban	3
Antiplatelets	
Aspirin	93
Clopidogrel	35
Cilostazol	31
Ticlopidine	12
Others	28
Anticoagulants + antiplatelets	28
Dual antiplatelets	59
Triple antiplatelets	8
Heparin bridge	73

thrombotic risk patients, intravenous unfractionated heparin (UFH) was administered after ceasing anticoagulants 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). Glyceol® (Chugai Pharmaceutical Co., Ltd.) and hyaluronic acid was used for submucosal injection in ESD. An electrosurgical unit (VIO 300D; ERBE, Tübingen, 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, hemoclipping, 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; anticoagulants 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 anticoagulants and antiplatelets were ceased before polypectomy except

Table 2 Characteristics of the study cohort and polyps *n* (%)

		No bleeding	Bleeding	<i>P</i> value
No. of patients		759 (96.3)	29 (3.7)	
Age (yr, mean)		64 ± 14.3	62 ± 16.0	0.50
Gender	Male	458 (98.1)	9 (1.9)	0.35
	Female	301 (93.8)	20 (6.2)	
Polyp location	Right	239 (95.6)	11 (4.4)	0.93
	Left	336 (95.5)	16 (4.5)	
Polyp size	≥ 10 mm	338 (96.8)	11 (3.2)	0.43
	< 10 mm	361 (95.8)	16 (4.2)	
Polyp shape	Flat	266 (96.7)	9 (3.3)	0.73
	Sessile	416 (96.5)	15 (3.5)	
	Pedunculated	118 (95.2)	6 (4.8)	
No. of polyps resected	1	343 (96.6)	12 (3.4)	0.69
	≥ 2	416 (96.1)	17 (3.9)	
Prophylactic clipping	Yes	566 (95.8)	25 (4.2)	0.16
	No	193 (98.0)	4 (2.0)	
Resection method	Polypectomy or EMR	703 (96.6)	25 (3.4)	0.20
	ESD	56 (93.3)	4 (6.7)	
Antiplatelets	Yes	146 (94.8)	8 (5.2)	0.27
	No	613 (96.7)	21 (3.3)	
Anticoagulants	Yes	72 (86.7)	11 (13.3)	< 0.001
	No	687 (97.4)	18 (2.6)	
Heparin bridge	Yes	63 (86.3)	10 (13.7)	< 0.001
	No	696 (97.3)	19 (2.7)	
Antiplatelets + heparin bridge	Yes	32 (91.4)	3 (8.6)	0.11
	No	727 (96.5)	26 (3.5)	
Anticoagulants + heparin bridge	Yes	47 (82.5)	10 (17.5)	< 0.001
	No	712 (97.4)	19 (2.6)	

PPB: Post-polypectomy bleeding.

Table 3 Multivariate analysis of risk factors for Post-polypectomy bleeding

Variable	Odds ratio	95%CI	<i>P</i> value
Anticoagulants	4.227	1.126-15.872	0.033
Heparin bridge therapy	2.172	0.556-8.482	0.265
Anticoagulants+ heparin bridge	9.796	3.771-25.443	< 0.001

PPB: Post-polypectomy bleeding.

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

Table 4 Summary of 11 post-polypectomy bleeding cases taking anticoagulants

	Anticoagu-lants	Antiplatelets	Heparin bridge	Onset of PPB (POD)	PT-INR at PPB	Anticoagulants at PPB	APTT at PPB	Heparin at PPB
1	Warfarin	Clopidogrel	Yes	5	1.62	Yes	93.1	Yes
2	Warfarin	-	Yes	2	1.31	Yes	42.8	Yes
3	Warfarin	-	Yes	6	1.26	Yes	32.2	No
4	Warfarin	Aspirin	Yes	2, 5	1.20	Yes	29.4	Yes
5	Warfarin	-	Yes	5	1.25	Yes	73.1	Yes
6	Dabigatran	-	No	2	2.03	-	-	-
7	Warfarin	-	Yes	1, 2	1.31	No	45.2	Yes
8	Dabigatran	-	Yes	6	1.40	-	50.1	No
9	Warfarin	-	Yes	1, 6	1.23	No	33.5	Yes
10	Warfarin	Aspirin (Continued)	Yes	2	1.32	Yes	40.4	Yes
11	Warfarin	-	Yes	1	1.21	Yes	29.5	Yes

PPB: Post-polypectomy bleeding; POD: Post-operative day.

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*^[5] demonstrated that resuming anticoagulants following polypectomy was strongly associated with severe delayed PPB. Witt *et al*^[13] 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*^[22] 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]. Yousefi *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*^[25] 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^[8]. 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%^[4-6], 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 antithrombotic 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.

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