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Colonic Postpolypectomy Bleeding Is Related to Polyp Size and Heparin Use

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Background/Aims: We studied factors influencing colon postpolypectomy bleeding (PPB), with a focus on antithrombotic and anticoagulation therapy.
Methods: We conducted a retrospective case-control study of all patients who underwent polypectomy at our tertiary referral center in Italy between 2007 and 2014. Polyp characteristics (number of polyps removed per patient, size, morphology, location, resection technique, prophylactic hemostasis methods) and patient characteristics (age, sex, comorbidities, medication) were analyzed.
Results: The case and control groups included 118 and 539 patients, respectively. The two groups differed in the frequency of comorbidities (69% vs. 40%, p=0.001), polyps removed (27% vs. 18%, p=0.02), and use of heparin therapy (23% vs. 1%, p<0.001). A total of 279 polyps in the case group and 966 in the control group were nonpedunculated (69% vs. 81%, p=0.01) and measured ≥10 mm (78% vs. 32%, p=0.001). Multivariate analysis showed that polyps ≥10 mm (odds ratio [OR], 6.1; 95% confidence interval [CI], 2.3–15.5), administration of heparin (OR, 16.5; 95% CI, 6.2–44), comorbidity (OR, 2.3; 95% CI, 1.4–3.9), and presence of ≥2 risk factors (OR, 3.2; 95% CI, 1.7–6.0) were associated with PPB.
Conclusions: The incidence of PPB increases with polyp size ≥10 mm, heparin use, comorbidity, and presence of ≥2 risk factors.
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Key Words: Postpolypectomy bleeding; Colonoscopy; Hemorrhage; Humans

INTRODUCTION

Endoscopic removal of adenomas is the optimal treatment for prevention of colorectal cancer because of minimal invasiveness and the low rate of procedure-related complications.[1]

Nonetheless, the reported rate of postpolypectomy bleeding (PPB) ranges from 0.07%–1.7%.[2-4] Previous studies identified some factors associated with PPB, including polyp size, location in the right colon, sessile morphology, number of polyps, comorbidities, endoscopist's experience, number of polyps removed, and use of antiplatelet and anticoagulant drugs.[4-12] European Society of Gastrointestinal Endoscopy (ESGE) guidelines state that polyps can be safely removed without interruption of aspirin therapy, but there is major debate about polyp removal without interruption of thienopyridines (ticlopidine, clopidogrel, prasugrel, and ticagrelor) and anticoagulants because of the paucity of data available about the safety of the procedure.[13] In contrast, an increased percentage of patients remain on these drugs because of a significant risk of ischemic events if medication is suspended. The American College of Chest Physicians (ACCP) guidelines recommend against suspension of dual antiplatelet therapy for 12 months following placement of a drug-eluting coronary stent, and advise administration of bridge therapy with low-molecular-weight heparin (LMWH) if oral anticoagulants are sus-

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pended, according to thrombotic risk.[14]

MATERIALS AND METHODS

The study was conducted according to the principles of the Declaration of Helsinki. A total of 14,580 medical charts of patients who underwent colonoscopic polypectomy from 2007 to 2014 were retrospectively reviewed (using computer-assisted research) in order to identify cases of immediate and delayed PPB. Immediate PPB was defined as intraprocedural hemorrhage. Delayed PPB was defined as occurring up to 30 days following polyp removal. The incidence of significant bleeding was calculated according to the International Society on Thrombosis and Haemostasis (ISTH)[15] definition (death, hemodynamic instability, drop of >2 g/dl of hemoglobin, need to repeat endoscopy with or without intervention, or need for >2 blood transfusion). Data were collected from clinical records including the nursing chart. Any suspension of antiplatelet drugs for less than 5 days was considered as "drugs not interrupted." Colonoscopic procedures were performed after suspension of LMWH (for at least 12 hours) and oral anticoagulants. Patients taking anti-vitamin K drugs interrupted therapy for 5 days before the procedure and received a therapeutic dose of LMWH when the international normalized ratio (INR) was <2; heparin was continued until a therapeutic INR level was restored after the procedure. Antiplatelet/anticoagulant agents were resumed after 48 hours if hemostasis was achieved. Emergency department clinical records were reviewed until 30 days following polypectomy to identify cases of PPB. Controls were selected from the same cohort of 14,580 patients, with a ratio of 1:4 (cases:controls). All consecutive patients who underwent polypectomy from March 2014 to June 2014 were included in the control group. Medical records with insufficient data for the patient or polyp characteristic were excluded. Removal of polyps was achieved with different modalities, but forceps biopsy was generally performed for polyps <5 mm, hot snare polypectomy for small sessile or pedunculated polyps, and endoscopic mucosal resection (EMR) for large sessile or pedunculated polyps. EMR technique consists of injection of submucosal adrenalin 1:20,000 with indigo carmine, followed by resection with snare polypectomy. From 2009 to 2014, a VIO 200D Erbe® (ERBE USA Inc, Marietta, GA, USA) electrosurgical unit was used at 2 different settings (Endocut Q3/Forced Coag effect 2 for small polyps and Endocut Q4/Forced Coag effect 2 for large polyps). The following data were reported for every patient: age, sex, comorbidities (cardiac, vascular, pulmonary, hepatic, neurologic, hematologic, neoplastic, or diabetic), use of antiplatelet drugs (aspirin, or thienopyridines such as ticlopidine, clopidogrel, prasugrel, or ticagrelor), use of LMWH, endoscopist, number of polyps removed, polyp characteristics (size measured with reference to an open biopsy forceps or an open snare, location, and morphology according to the Paris Classification),[16] removal technique (cold biopsy, diathermic snare coagulation, or EMR), prophylactic measures for bleeding (metallic clip, Endoloop®, Over the Scope Clip OTSC®), days from endoscopic procedure to presentation of bleeding, cases of major bleeding, and treatment of bleeding.

Statistics

Continuous and categorical variables were expressed as mean±standard deviation, and frequencies were expressed as percentage, odds ratio (OR), and 5%–95% confidence interval (CI). Comparisons for univariate analysis were made with the chi-square test for categorical variables and student's *t*-test for continuous variables. Variables with *p*-value <0.1 were included in the stepwise multivariate logistic regression model. Statistics was performed with STATA 13 software (StataCorp, College Station, TX, USA).

RESULTS

After removal of 279 polyps, 118 patients experienced bleeding (27% of patients had ≥3 polyps). PPB was immediate or late in 41% and 59%, respectively. The incidence of PPB was 0.8% per year over a period of 7 years. The median time from polypectomy to onset of symptoms was 2.5 days. Compared with immediate bleeding, delayed bleeding was associated with the presence of major bleeding (44% vs. 25%, p=0.03), use of LMWH (30% vs. 12%, p=0.03), and presence of any comorbidity (77% vs. 53%, p=0.03). Among patients with PPB, 36 underwent colonoscopy without any endoscopic interventions, 80 received injective and/or mechanical hemostasis during endoscopy, and 2 went to surgery because of persistent and severe bleeding. There were no deaths related to PPB. The control group included 539 patients and a total of 966 polypectomies (18% had ≥3 polyps). Characteristics were grouped when there were less than 10 cases (nonsteroidal anti-inflammatory drugs with aspirin, Endoloop® and OTSC® with hemoclip, direct anticoagulant drugs with heparin). Compared with controls, patients with PPB had more comorbidities (69% vs. 40%, p=0.001), more polyps (27% of patients with ≥3 polyps vs. 18%, p=0.02), and underwent polypectomy more frequently without interruption of LMWH (22% vs. 1%, p=0.001). Polyps with PPB were predominantly nonpedunculated (69% vs. 81%, p=0.02) and were larger than those from patients without PPB (78% of polyps were ≥10 mm vs. 32%, p=0.001). There were no significant differences in the factors

Table 1. Characteristics of the Patients (Cases versus Controls)

	Bleed (%)	No bleed (%)	*p*-value	OR (CI 5%–95%)
Number of patients	118	539		
Age, yr	67±12	65±10	0.138	
Age ≥65	63 (53)	309 (57)	0.434	0.8 (0.6–1.3)
Males	77 (65)	336 (62)	0.568	1.1 (0.7–1.7)
Antiplatelet/anticoagulant				
None	70 (59)	467 (87)	0.001	0.2 (0.1–0.3)
Aspirin	12 (10)	32 (6)	0.096	1.8 (0.9–3.6)
Thienopyridines	6 (5)	25 (5)	0.836	1.1 (0.4–2.7)
Dual APA	3 (2)	8 (1)	0.417	1.7 (1.4–6.6)
LMWH	27 (22)	7 (1)	0.001	22.5 (9.5–53.3)
Any comorbidity	82 (69)	214 (40)	0.001	3.4 (2.2–5.3)
Polyps	279	966		
Polyp's characteristics				
≥10 mm	92 (78)	176 (32)	0.001	7.3 (4.6–11.7)
Non-pedunculated	81 (69)	440 (81)	0.002	0.5 (0.3–0.8)
Right colon	56 (47)	211 (39)	0.096	1.4 (0.9–2.1)
Patients ≥3 polyps	32 (27)	97 (18)	0.024	1.7 (1.1–2.7)
Resection characteristics				
Biopsy forceps	5 (4)	234 (43)	0.001	0.06 (0.02–0.1)
Snare polypectomy	30 (25)	128 (24)	0.700	1.1 (0.7–1.7)
EMR	83 (70)	177 (33)	0.001	8 (3.1–7.4)
Clip	88 (75)	185 (34)	0.001	5.6 (3.5–8.8)
Patient ≥1 risk factor[a)]	88 (75)	140 (26)	0.001	8.4 (5.2–13.2)
Patients ≥2 risk factors[a)]	43 (36)	37 (7)	0.001	7.8 (4.7–12.8)

OR, odds ratio; CI, confidence interval; APA, antiplatelet agents; LMWH, low-molecular-weight heparin; EMR, endoscopic mucosal resection.
[a)]Continuous and categorical variables were expressed as mean±standard deviation and frequencies with percentage, OR and CI 5%–95% respectively.

associated with the 10 endoscopists who performed the polypectomies in the 2 groups (data not shown). In the univariate analysis, some covariate interactions were introduced by the number of patients with ≥1 or ≥2 risk factors for PPB (factors with *p*-value <0.05), in order to highlight adjunctive risk factors. Because polyps in the PPB group were mainly large and nonpedunculated, EMR with clip placement was the most common resection technique, as compared with controls (EMR, 70% vs. 33%, *p*-value 0.001; clip placement, 75% vs. 34%, *p*-value 0.001). Patient characteristics and results of univariate analysis are shown in Tables 1 and 2. Multivariate analysis showed that polyps ≥10 mm, administration of LMWH, any comorbidity, and presence ≥2 risk factors were associated with PPB (Table 3).

DISCUSSION

This retrospective case-control study found that PPB is influenced by polyp size ≥10 mm, administration of LMWH, presence of any comorbidity, and presence of ≥2 risk factors. Results from previous studies of risk factors for PPB are heterogeneous because of their prospective or retrospective nature, differences in the characteristics of the polyps or patients, and risk factors considered. Polyp size was the major risk factor identified in a large number of studies.[5-9,11] A large lesion is more vascular than a small polyp and vessels are larger in diameter. There is no clear evidence for an association between antiplatelet and anticoagulant drug use and PPB. Most studies stated that aspirin is not a risk factor for PPB.[5,10,12,17,18] In a retrospective survey, Pan et al. showed a significant association between PPB and aspirin, but not with nonsteroidal anti-in-

Table 2. Immediate Post-Polypectomy Bleeding versus Delayed Post-Polypectomy Bleeding

	Immediate bleeding (%)	Delayed bleeding (%)	*p*-value	OR (CI 5%–95%)
Number of patients	48 (41)	70 (59)		
Age, yr	65.5±12.7	68.1±12.2	0.378	
Males	28 (58)	49 (70)	0.191	0.6 (0.3–1.3)
Antiplatelet/anticoagulant				
None	38 (92)	32 (46)	<0.001	5.7 (2.5–13.0)
Aspirin	2 (4)	10 (14)	0.09	0.3 (0.1–1.2)
Thyenopiridines	2 (4)	4 (6)	0.074	0.7 (0.1–4.0)
Dual APA	0	3 (4)	0.146	0.2 (0.1–0.9)
LMWH	6 (12)	21 (30)	0.026	3 (1.1–8.1)
Any comorbidity	28 (53)	54 (77)	0.030	2.4 (1.1–5.4)
Polyp's characteristics				
≥10 mm	40 (83)	52 (74)	0.244	1.7 (0.7–4.3)
Non-pedunculated	33 (69)	48 (69)	0.984	1.8 (0.8–4.0)
Right colon	23 (48)	33 (47)	0.9	1 (0.5–2)
Patients ≥3 polyps	14 (29)	18 (26)	0.5	1.3 (0.6–3.1)
Resection characteristics				
Biopsy forceps	4 (8)	1 (1)	0.934	6.2 (0.7–57.9)
Snare polypectomy	4 (8)	26 (37)	0.001	0.1 (0.1–0.4)
EMR	40 (84)	43 (62)	0.010	3.1 (1.3–7.7)
Patient ≥1 risk factor[a)]	33 (69)	55 (79)	0.229	0.6 (0.4–1.4)
Patients ≥2 risk factors[a)]	7 (15)	21 (30)	0.053	0.4 (0.1–1.0)
Bleeding characteristics				
Major bleeding	12 (25)	31 (44)	0.032	2.3 (1.1–5.3)
Endoscopy without hemostasis	11 (23)	25 (35)	0.138	0.5 (0.2–1.2)
Endoscopy with hemostasis	36 (75)	44 (63)	0.166	1.8 (0.8–3.9)
Surgery	1 (2)	1 (2)	0.787	1.5 (0.1–24.0)

OR, odds ratio; CI, confidence interval; APA, antiplatelet agents; LMWH, low-molecular-weight heparin; EMR, endoscopic mucosal resection.
[a)]Continuous and categorical variables were expressed as mean±standard deviation and frequencies with percentage, OR and CI 5%–95% respectively.

flammatory drugs.[19] Metz et al. showed a significant association between PPB and aspirin, but the study was conducted on large colonic lesions.[20] According to evidence from a meta-analysis,[21] thienopyridines such as clopidogrel increase the risk of delayed PPB (pooled relative risk for PPB of 2.54; 95% CI, 1.68–3.84; $p<0.00001$). ESGE guidelines recommend interruption of thienopyridines before polypectomy only if the patient had no recent thrombotic event or a coronary drug-eluting stent placed >12 months previously.[13] ESGE guidelines state: "If antiplatelet or anticoagulant therapy is discontinued, then we recommend this should be resumed up to 48 hours after the procedure depending on the perceived bleeding and thrombotic risks." Our study supports these recommendations, even though this sample did not include a large number of patients using these drugs. Another limitation of this study is the possible underestimation of the incidence of PPB cases, and especially those with minor bleeding. Some patients may have been treated at other hospitals, whose medical charts were not accessible, or patients with only minor bleeding may not have gone to the emergency room. An additional limitation of our study, because of its retrospective nature, is the underestimation of the possible role played by antiplatelet drugs in PPB, because these agents are sometimes interrupted after polypectomy. The data on use of these drugs in PPB cases after polypectomy were always available from the medical charts, but the data for controls were unclear (recall bias).

Table 3. Multivariate Logistic Regression Analysis

Variable	OR (CI 5%–95%)	*p*-value
No antiplatelet/ anticoagulant theraphy	1.2 (0.5–3.5)	0.618
Aspirin	1.8 (0.5–5.8)	0.350
LMWH	17.3 (4.5–65.9)	<0.001
Polyp ≥10 mm	2.6 (1.2–5.7)	0.013
Number of polyps ≥3	1.2 (0.6–2.4)	0.547
Non-pedunculated	0.8 (0.4–1.4)	0.468
Right colon	1.7 (0.9–2.9)	0.061
Any comorbidity	1.9 (0.9–3.9)	0.080
EMR	1.0 (0.3–3.0)	0.956
Clip	1.4 (0.5–4.2)	0.524
≥1 Risk factor	1.5 (0.6–3.7)	0.378
≥2 Risk factors	3.2 (1.6–6.3)	0.010

OR, odds ratio; CI, confidence interval; LMWH, low-molecular-weight heparin; EMR, endoscopic mucosal resection.

Conversely, LMWH was always administered before and after the procedure (bridge therapy) because of the known risk of thromboembolism in the absence of the drug. This study clearly showed the association between heparin bridge therapy and risk of PPB, and especially for delayed PPB. In previous studies, Witt and Inoue observed more bleeding episodes in patients who received polypectomy with use of heparin or heparin bridge therapy.[22,23] The BRIDGE and PERIOP-2 randomized, prospective, placebo-controlled trials evaluated strategies for periprocedural management of anticoagulant drugs. According to recent evidence, bridging therapy should be avoided in patients at low risk of thrombosis; the need for bridging therapy and the timing of post-procedure anticoagulation should be balanced according to the thrombotic and bleeding risk.[24,25] The thrombotic risk is currently assessed with the CHA2DS2-VASc score;[26] similarly, PPB risk should be assessed by taking into account not only medication use or polyp size alone, but all risk factors, as shown in our study.

It is essential to keep in mind that preventive clipping or endoloop use is warranted in polypectomy, even though one retrospective study failed to show a protective role of clipping in patients taking antiplatelet/anticoagulant drugs.[27] With regard to prophylaxis, one meta-analysis showed that injective or mechanical measures are effective at reducing early PPB but not late PPB.[28] Another meta-analysis[29] that considered only large polyps showed a reduction in PPB risk with adrenaline injection or mechanical hemostasis (mainly loop). Our study failed to establish a protective role for metallic clips; however, our univariate analysis showed that hemoclips were more frequently used in PPB cases than in controls because of the relatively larger size of lesions resected in the case group. According to a cost-effectiveness decision analysis, the placement of a prophylactic endoscopic clip after polypectomy appears to be an appropriate strategy for patients who receive antiplatelet or anticoagulation therapy.[30] In conclusion, the size of the resected polyp, use of LMWH, comorbidities, and presence of ≥2 risk factors were independently correlated with PPB. Periprocedural management decisions should be based on assessment of competing risks for thrombosis and bleeding.

Conflicts of Interest

The authors have no financial conflicts of interest.

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