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Serum C-reactive protein as a possible marker to predict delayed hemorrhage after colonoscopic polypectomy

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Summary

Background:	Post-polypectomy hemorrhage is one of the complications of colonoscopic polypectomy. And there is no definitive and convenient laboratory test that could be used to predict risk of delayed post-polypectomy hemorrhage. This research aimed to study risk prediction of delayed post-polypectomy hemorrhage using serum C-reactive protein (CRP) level as a marker.
Material/Methods:	In a retrospective, case-controlled study, 302 cases of post-polypectomy patients were divided into hemorrhage group and non-hemorrhage group. The CRP levels 24-hours after colonoscopic treatment were compared between the two groups to assess whether elevated serum CRP levels in addition to other risk factors such as age, gender, smoking, alcohol consumption, hypertension (AHT) and size of polyps may predict risk of delayed post-polypectomy hemorrhage.
Results:	The hemorrhage group had significantly higher levels of serum CRP (32.50 ± 17.34 mg/L <i>vs.</i> 6.32 ± 6.02 mg/dL) and were also having a higher incidence of hypertension compared to the non-hemorrhage group (both $P < 0.05$). Patients with elevated serum CRP levels (≥ 10 mg/L) after colonoscopic treatment are at a higher risk of developing post-polypectomy hemorrhage (OR 1.329, 95%CI 1.125–1.571) as compared with patients whose CRP levels were not increased.
Conclusions:	A higher level of serum CRP may serve as an indicator of delayed post-polypectomy hemorrhage and there appears to be a direct relationship between the serum CRP levels and the risk of post-polypectomy hemorrhage: the higher CRP levels the higher the risk of post-polypectomy hemorrhage.
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BACKGROUND

Coloscopic polypectomy is an effective approach for the treatment of colorectal polypoid lesions. Resection of potential malignant adenomas reduced the risk and incidence of colon cancer. However, coloscopic polypectomy is not without complications and the most frequent being post-polypectomy hemorrhage. A 1–3% incidence rate of hemorrhage after colonoscopy polypectomy is considered as reasonable [1–3], while a higher incidence of 3–10% is known to occur following endoscopic mucosal resection (EMR) and endoscopic submucosal dissection [4–6]. The occurrence of hemorrhage is most common during and immediately after the procedure though it is unlikely to cause significant clinical consequences if the patients are closely monitored. But, in an occasional instance, hemorrhage could occur several days after polypectomy that can be potentially serious and sometimes even life threatening. Delayed post-polypectomy hemorrhage is defined as hemorrhage occurring 24 hours after the colonoscopic treatment that occurs in approximately 2% of all patients [7,8]. Several risk factors of delayed post-polypectomy hemorrhage have been identified that include: polyps-related factors such as large size and sessile form, and patients-related factors such as hypertension [7–9]. However, there is no definitive and convenient laboratory test that could be used to predict risk of delayed post-polypectomy hemorrhage. In this study, we evaluated the efficacy of serum C-reactive protein (CRP) that is a sensitive biomarker for bacterial infection, inflammation, infarction and injury to predict the occurrence of delayed post-polypectomy hemorrhage.

MATERIAL AND METHODS

Patients

We performed a case-control study of 302 patients who underwent colonoscopic polypectomy from January 2004 to November 2009. Detailed medical records were reviewed, including size and location of polyps removed, macroscopic type of polyps, histopathological findings, resection methods, presence or absence of delayed hemorrhage and clinical characteristics of patients. Written consent was taken from each patient according to the Ethics Committee of School of medicine, Zhejiang University.

The following exclusion criteria were used in our study: (1) hemorrhagic disorders, a recent history of taking anticoagulants or anti-platelet drugs, or abnormal result of coagulation tests (platelet count less than 100,000/mL or prothrombin time longer than 12 second, within 2 weeks prior to colonoscopy). (2) Presence of recent surgery, trauma, febrile disorders, acute or chronic inflammatory disease, autoimmune diseases, or a prior myocardial infarction (MI) and acute coronary syndrome (ACS). (3) Presence of polypoid syndrome. Furthermore, patients older than 60 years or those with known heart disease were advised to have made electrocardiographic examination (ECG) before treatment and were continuously monitored while undergoing treatment. Long term users of anticoagulants or anti-platelet drugs were asked to stop these medications for 1 week prior to polypectomy. Patients with hypertension were included in the study only if blood pressure is below 140/90mmHg prior to treatment.

Follow-up and dietary advise

All patients were kept under close observation for 4 hours immediately after colonoscopic polypectomy in the event of immediate bleeding and were followed-up for the next 14 days by telephone contact. Follow-up for a period of 2 weeks from the day of polypectomy was achieved of all patients included in the study. Delayed postpolypectomy bleeding was defined as occurrence of tarry stool and/or bleeding during the follow-up period. All patients with tarry stool and/or bleeding should go through a second colonoscopy to confirm the reason and location of hemorrhage.

All patients who underwent colonoscopic polypectomy were advised to follow strict diet control that included absolute abstain from alcohol and avoidance of food rich in protein or fat for 2 weeks. In addition, these patients were also advised to avoid intense physical activity and long-distance travel.

Colon preparation and polypectomy methods

Colon preparation was conducted using polyethylene glycol electrolyte solution. Three resection approaches were used according to the size and macroscopic appearance of polyps. Polyps that were less than 0.5 cm were removed using hot biopsy; protruding polyps of less than 2.5 cm in size were resected by snare polypectomy; broad-based polyps that were less than 2 cm and IIc lesions (slightly depressed without ulcer) were treated by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) methods; pedicled polyps which were larger than 2.5 cm were resected by snare polypectomy [9–11]. The treatment for sessile polyps larger than 2.5 cm were determined according to the mucosal pit pattern classification. EMR was chosen if canceration was excluded, otherwise we would choose ESD for polyps with cancerous tendency pit pattern. Additional surgery was employed if endoscopic treatment failed.

All colonoscopic polypectomies were performed by one experienced endoscopist. The nurses all had standard training and did the snare following close instructions of the endoscopist. To reduce current of injury as much as possible, conduction time was regulated for different types of polyps.

Definitions of polyp-associated and patient-associated factors

The polyp size was determined by comparing to open forceps (5 mm) before polypectomy. The macroscopic type was classified based on the criteria of the Paris endoscopic classification of superficial neoplastic lesions [12]. Hypertension was defined as systolic/diastolic blood pressure of $\geq 140/90$ mmHg (according to the criteria of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [13]; those who smoke daily for over 6 months were defined as smokers according to WHO suggestions for standard smoking investigation methods, and alcohol consumption was considered to be present when the subject consumed 5 or more drinks per week as previously described.

CRP assay

Three milliliter peripheral blood was drawn to detect CRP level for each patient 24 hours after colonoscopic polypectomy.

Table 1. General information of colorectal polyps and CRP levels after treatment.

Spectrum of diseases	No. of patients	Macroscopic type of polyp						Size of polyp (cm)	Treatment	Mean CRP value (mg/L)	
		Protruding			Flat		Depressed				
		Is	Isp	Ip	Ila	LST	Ilc				Ilc+Ila
Colorectal cancer	5		1		1		1	2	1.68±0.80 (0.4~2.5)	EMR or ESD	5.78±2.13
Adenomatous polyps	258	89	72	42	34	19	1	1	0.99±0.70 (0.4~3.5)	Hot biopsy polypectomy EMR or ESD	7.40±8.48
Hyperplastic polyps	32	6	9	4	10	3			0.75±0.32 (0.4~1.5)	Polypectomy EMR	6.01±6.33
Juvenile polyps	7	2	2	2	1				1.36±1.02 (0.6~3.0)	Polypectomy	5.87±2.45

The normal reference range for the assay is <10.0 mg/L. We monitored CRP level of patients with delayed post-polypectomy bleeding or elevated CRP value (CRP >10mg/L) once in every 1~3 days until bleeding was controlled or CRP value returned to normal. Serum CRP level was determined using immunoturbidimetry method with an automatic biochemical analyzer (OLYMPUS AU5400, JAPAN).

Statistical analysis

Statistical analysis was performed by SPSS 16.0 software for Windows XP system. Data were expressed as mean ± standard deviation (SD). Independent Sample T-test was performed to analyze quantitative data and qualitative data was analyzed by Chi square test. Logistic regression including variables with P-value less than 0.05. The variables in this study were: age, sex, smoking, alcohol, hypertension disease, size, type and location of polyps and CRP level. Confidence intervals (CIs) were set for the 95% level and statistical significance was indicated if P value was less than 0.05.

RESULTS

Baseline characteristics of patients and polyps in the study

302 patients with lesions were included in the study, averaging 56±13 years old; of all the patients, 181 (59.9%) were male, 59 (19.5%) were smokers and 40 (13.2%) were alcohol consumers; 47 (15.6%) have arterial hypertension (AHT), the average CRP level is 7.18±8.12 mg/L.

All the 302 Patients received endoscopic treatment. Of all, 258 were having adenoma, while 32 had hyperplastic polyps, 7 juvenile polyps and 5 colorectal cancer (Table 1).

Of all 302 patients studied, CRP was raised in 46 (15.2%). Delayed post-polypectomy hemorrhage occurred in 10 (3.3%) and their CRP level ranged from 14.8 mg/L to 64.0 mg/L with an average of 32.50±17.34 mg/L.

Risk factors for delayed post-polypectomy bleeding

Patients with hemorrhage had significantly higher levels of CRP value (32.50±17.34mg/L *vs.* 6.32±6.02 mg/L; P<0.05),

compared with the non-hemorrhage group. It was also observed that a higher incidence of hypertension in those who had post-polypectomy hemorrhage compared with those who did not have hemorrhage (P<0.05). No significant differences were found between the two groups with respect to age, gender, smoking, alcohol consuming, size, type and location of polyps (Table 2).

Logistic regression analysis showed that raised CRP value is a significant risk factor that predicts the development of post-resection hemorrhage with an odds ratio of 1.329(95% CI, 1.125–1.571) (P<0.001, Table 3). Presence of hypertension was not significant in the logistic regression analysis.

Dynamic monitoring of CRP level in patients with elevated CRP values

In order to know dynamic relationship between serum CRP levels and development of post-polypectomy hemorrhage, we monitored serum CRP levels in 46 cases with elevated CRP values (CRP >10 mg/L) once in every 1~3 days. It was noted that serum CRP values began to increase on the first day of treatment and returned to normal within 2~13 days (average 4±2 days).

While comparing patients with elevated CRP values, we noted that CRP levels were higher in hemorrhage group than in non-hemorrhage (32.50±17.34 mg/L *vs.* 18.72±7.62 mg/L, P<0.05, Table 4), and it took more time for CRP levels returning to normal in those with post-polypectomy hemorrhage than those without hemorrhage (6±3 days *vs.* 4±2 days, P<0.05, Table 4). It was noted that serum CRP levels returned to normal even in those who had post-polypectomy hemorrhage once the hemorrhage ceased.

Treatment of patients with elevated CRP level

There were 10 patients who had late-phase delayed bleeding, the details of which are given in Table 5. Post-polypectomy hemorrhage was seen within two weeks of therapy. In all patients, hemorrhages could be controlled in time without any complications. In all these patients with or without hemorrhage CRP decreased to normal within two weeks.

Table 2. Univariate analysis between patients with hemorrhage and without hemorrhage.

Variables	No hemorrhage	Hemorrhage	Univariate P value
No.	292	10	
Gender (male/female)	131/85	7/3	0.510
Mean age (years)	56±13	63±11	0.089
Smoking	55 (18.8%)	4 (40.0%)	0.098
Alcohol	38 (13.0%)	2 (20.0%)	0.523
Hypertension	42 (14.4%)	5 (50.0%)	0.002
Size of polyps (cm)	1.01±0.84	1.24±0.61	0.386
Location of polyps			0.376
Ileocecal junction	14	0	
Ascending colon	53	0	
Transverse colon (including hepatic flexure and splenic flexure)	64	3	
Decending colon	52	4	
Sigmoid colon	65	2	
Rectum	44	1	
Macroscopic type of polyp			0.103
Protruding(Is, lsp, lp)	224	5	
Flat(IIa, LST)	63	5	
Depressed(IIc, IIa+IIc, IIc+IIa)	5	0	
Histopathology of polyp			0.623
Colorectal Cancer	5	0	
Adenomatous Polyps	248	10	
Hyperplastic Polyps	32	0	
Juvenile Polyps	7	0	
CRP values (mg/L)	6.32±6.02	32.50±17.34	<0.001

Table 3. Multivariate logistic regression analysis for risk factors of hemorrhage after colonoscopic treatment.

Variables	Odds ratio	95% Confidence Interval	P value
Hypertension	0.984	0.099–9.763	0.989
CRP value (mg/L)	1.329	1.125–1.571	<0.001

Table 4. Univariate analysis in patients with elevated CRP values.

Variables	No hemorrhage	Hemorrhage	Univariate P value
CRP values (mg/L)	18.72±7.62	32.50±17.34	<0.05
Time for CRP to return to normal (day)	4±2	6±3	<0.05

Table 5. Details of the ten patients with delayed post-polypectomy hemorrhage.

No.	Sex	Age	Treatment	Complication	Causes of complication	Polyp type	Site of polyp	Size of polype (cm)	Histopathology
1	Male	67	Colon polypectomy	Delayed hemorrhage	Intaking food too early	Ila	Transverse colon	0.5	Adenoma
2	Male	67	EMR	Delayed hemorrhage	Intaking food too early	LST	Transverse colon	2.5	Adenoma
3	Male	74	Colon polypectomy	Delayed hemorrhage	Long term antihypertensive vasodilator grugs administration due to AHT	Is	Sigmoid colon	0.7	Adenoma
4	Male	67	Colon polypectomy	Delayed hemorrhage	Intense movement after endoscopic therapy too early	Is	Transverse colon	1.2	Adenoma
5	Female	41	Colon polypectomy	Delayed hemorrhage	Long term grug administration of hydrocortisone due to SLE	Ila	Descending colon	0.8	Adenoma
6	Female	61	Colon polypectomy	Delayed hemorrhage	Long term antihypertensive vasodilator grugs administration due to AHT	Ila	Descending colon	1.5	Adenoma
7	Male	57	EMR	Delayed hemorrhage	Muscular propria injured by endoscopic therapy	Ila	Sigmoid colon	1	Adenoma
8	Male	81	Colon polypectomy	Delayed hemorrhage	Long term antihypertensive vasodilator grugs administration due to AHT	Isp	Descending colon	1	Adenoma
9	Male	57	Colon polypectomy	Delayed hemorrhage	Long term antihypertensive vasodilator grugs administration due to AHT	Is	Rectum	1.2	Adenoma
10	Female	56	EMR	Delayed hemorrhage	Polype base containing pulsatile vessel	Ip	Hepatic flexure of colon	2	Adenoma with moderate dysplasia

DISCUSSION

C-reactive protein (CRP) is an acute phase reactant synthesized by liver that has a regulatory role on other inflammatory markers such as IL-2, IL-6, TNF- α , is one kind of sensitive marker of inflammation and tissue injury [14–17]. CRP is considered as a valuable predictor of occurrence and prognosis of myocardial infarction (MI), acute coronary syndrome (ACS) and other cardiovascular diseases [18–20]. Recent studies revealed that CRP has a role in the pathobiology of thrombosis and may modulate the behavior of endothelial progenitor cells (EPCs). *In vitro* experiments revealed that CRP inhibited vasodilatation by attenuating the release of endothelial nitric oxide (eNO) [21,22]; Verma S et al. observed that human recombinant CRP directly inhibited EPC differentiation, survival, and function,

key components of angiogenesis. Thus, those with chronic ischemia with elevated levels of CRP may have compromised eNO production and attenuated proliferation of EPC that may impede healing process [22]. This is supported by the observation that mice with elevated levels of CRP showed a significantly faster and higher rate of arterial thrombosis [23]. Furthermore, volunteers receiving recombinant human CRP (rh-CRP) showed inappropriately activated coagulation system [24].

Mechanism(s) of delayed post-polypectomy hemorrhage is not known. There are no reliable indicators to predict the occurrence of delayed hemorrhage. Although location and size of polyps were regarded to be risk indicators for delayed post-polypectomy hemorrhage [7,8], while our data didn't show significant relationship between location or size of

polyps and post-polypectomy hemorrhage. The results of the present study revealed that those with significantly elevated plasma CRP levels had delayed post-polypectomy hemorrhage compared to those without delayed post-polypectomy hemorrhage. Logistic regression analysis showed that CRP value was a significant risk factor with a high predictive value with an odds ratio of 1.329 (95% CI, 1.125–1.571) ($P < 0.001$). Hence, we regard elevated CRP values within 24 hrs after polypectomy is a reliable indicator and predictor of delayed post-polypectomy hemorrhage.

CONCLUSIONS

Based on the results of the present study, we propose that CRP is synthesized by the liver in response to vascular injury caused by polypectomy and a high CRP level 24 hours after treatment may suggest that vascular injury is incompletely repaired with potential risk of hemorrhage.

Hence, it is suggested that serum CRP level could be used as a surveillance marker to predict hemorrhage after colonoscopic treatment.

Conflict of interest

All the authors declare that they have no conflict of interest.

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