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RAPID COMMUNICATION

Comparison of postpolypectomy bleeding between epinephrine and saline submucosal injection for large colon polyps by conventional polypectomy: A prospective randomized, multicenter study

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Abstract

AIM: To evaluate and compare the clinical outcomes of prophylactic submucosal saline-epinephrine injection and saline injection alone for large colon polyps by conventional polypectomy.

METHODS: A prospective study was conducted from July 2003 to July 2004 at 11 tertiary endoscopic centers. Large colon polyps (> 10 mm in diameter) were randomized to undergo endoscopic polypectomy with submucosal saline-epinephrine injection (epinephrine group) or normal saline injection (saline group). Endoscopic polypectomy was performed by the conventional snare method, and early (< 12 h) and late bleeding complications (12 h-30 d) were observed.

RESULTS: A total of 561 polyps in 486 patients were resected by endoscopic polypectomy. Overall, bleeding complications occurred in 7.6% (37/486) of the patients, including 4.9% (12/244) in the epinephrine group, and 10.3% (25/242) in the saline group. Early and late postpolypectomy bleeding (PPB) occurred in 6.6% (32/486) and 1% (5/486) of the patients, respectively, including 4.5% (11/244), 0.4% (1/244) in the epinephrine group, and 8.7% (21/242), 1.7% (4/242) in the saline group. No significant differences in the rates of overall, early and late PPB were observed between the 2 groups. Multivariate stepwise logistic regression analysis revealed that large size (> 2 cm) and neoplastic polyps were independently and significantly associated with the presence of PPB.

CONCLUSION: The prophylactic submucosal injection of diluted epinephrine does not appear to provide an additional advantage over the saline injection alone for the prevention of PPB.

Key words: Colonoscopic polypectomy; Bleeding; submucosal injection; Saline; Epinephrine

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INTRODUCTION

Colonoscopic polypectomy effectively reduces the risk of colorectal cancer[1-3]. The major complication of this procedure is hemorrhage, the occurrence of which varies between 0.3% and 6.1%, following perforation and problems with premedication[1-5]. It was reported that a submucosal saline solution injection is used for at least some polyps by 82% of physicians[6]. This submucosal saline cushion has been used to reduce postpolypectomy complications and enhance complete resection[7,8]. Local epinephrine has also been used to minimize mucosal bleeding due to its hemostatic effect, but its clinical benefit may not be clear. One prospective comparative study reported that epinephrine in the submucosal injection fluid could reduce the risk of immediate bleeding but not delayed bleeding[9]. In an American Society for Gastrointestinal Endoscopy (ASGE) editorial, because the overall risk of immediate bleeding is low and the immediate bleeding can generally be treated successfully by experienced endoscopists, there is no mandate to include epinephrine in the injection fluid[10]. The purpose of the current prospective multicenter study was to evaluate and compare the clinical outcomes of prophylactic submucosal saline-epinephrine injection and saline injection alone in conventional colon polypectomy.

MATERIALS AND METHODS

Between July 2003 and May 2004, patients diagnosed with colon polyps with a diameter > 10 mm were randomized to receive either a submucosal saline-epinephrine injection (epinephrine group) or a normal saline injection (saline group) before conventional polypectomy. The following exclusion criteria were used in the study: (1) diameter of polyp < 1 cm, (2) diameter of polyp larger than the size of a polypectomy snare requiring the submucosal dissection method, (3) patients taking anticoagulants, (4) disease impairing normal blood clotting, (5) abnormal coagulogram (platelet count, INR, APTT), (6) patients unwilling to give written informed consent, (7) age < 18 years. The trial profile is shown in Figure 1. All colonoscopies were performed with an Olympus CF-230 or CF-240 video colonoscope, after careful preparatory cleansing of the bowel using a polyethylene glycol-electrolyte solution. Midazolam was given intravenously only if needed. Patients were randomized using computerized randomization. The result of the randomization was kept blind from the endoscopist and the assistant. A submucosal injection solution was made in advance by the 2nd assistant. The Korean Association for the Study of Intestinal Diseases (KASID) approved the design of the trial. Informed consent was obtained from every enrolled patient before each procedure. If a patient had more than one polyp, all the polyps fulfilling the inclusion criteria were selected for prophylactic injections according to randomization.

In each group, injections of 0.01% epinephrine or normal saline were administered into the polyp stalk or base using a flexible needle injector, before resection with a standard snare. A total of 2-25 mL of solution was injected in this study. The injection volume was determined by observation of tissue elevation sufficient to perform polypectomy safely and completely. Polypectomy was executed according to the conventional method. The polyps were snared with a diathermic snare, linked to an electrocoagulator. The polyps were removed by bipolar electrocauterization, using a blended current (setting power: 30-40 Watts) only. If the remaining tissue was under suspicion, the procedure was repeated until resection was complete. After colonoscopic polypectomy, patients were nonhospitalized, or hospitalized for observation for 24 h. Early bleeding was defined as hematochezia within 12 h of the procedure, and late bleeding as bleeding occurring 12 h-30 d after the endoscopic procedure.

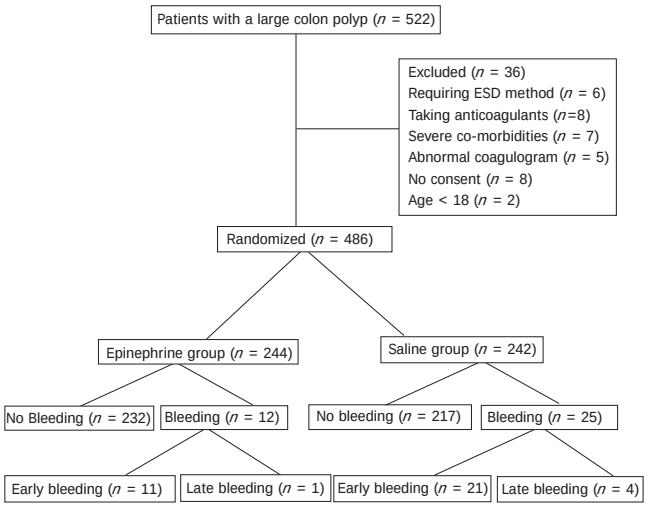

Figure 1 Flow of study participants.

The data were analyzed in several subgroups within each main group, according to the size, shape (protruding type: sessile, semipedunculated, pedunculated or superficial elevated type), and distribution of polyp (left colon, right colon or both).

Histologic studies were performed on all removed polyps. The resected polyps were fixed and embedded in paraffin. Serial sections, perpendicular to the mucosal surface, were obtained and stained with hematoxylin and eosin. The data were analyzed by their histologic features as nonneoplastic or neoplastic (dysplasia, high grade dysplasia or carcinoma *in situ*, cancer). We determined our sample size by assuming that submucosal saline-epinephrine injection solution would reduce the bleeding rate by 10%-20%, based on various reports of the rates of PPB. Given $\alpha = 0.05$, a power of 80%, we required a sample size of 450 patients. Data were analyzed by using Statistical Package for the Social Sciences program (version 6.12, SAS Institute Inc, Cary, NC). Categorical variables were compared by using the chi-square test. When two variables were dichotomous, the Fisher's exact test was used. To evaluate the continuous variables, Student's *t* test was used. Multivariate logistic regression analyses were performed for the risk factor of PPB. $P < 0.05$ was considered statistically significant.

RESULTS

In a total of 486 patients, 561 polyps were resected by endoscopic polypectomy. The median age of the patients

Table 1 Baseline characteristics of the studied patients

	Epinephrine group (n = 244)	Normal saline group (n = 242)	P
Clinical features			
Age (mean ± SD)	56.0 ± 11.4	56.8 ± 11.3	0.429
Sex (Male%)	195 (70.9%)	184 (64.3%)	0.096
BMI (mean ± SD)	23.0 ± 2.9	23.8 ± 2.7	0.572
Endoscopic features			
Total No. of polyps	275	286	0.587
Mean No. of polyps	1.13 ± 1.6	1.18 ± 2.0	0.149
Mean size of polyps (mm)	14.5 ± 5.7	15.0 ± 6.8	0.318
Macroscopic form of polyps			0.427
Pedunculated (Ip)	62 (22.5%)	66 (23.1%)	
Semipedunculated (Isp)	93 (33.8%)	107 (37.4%)	
Sessile (Is)	70 (25.5%)	80 (28.0%)	
Superficial elevated type (Ⅱa)	50 (18.1%)	33 (11.5%)	
Distribution of polyps			0.809
Left colon (descending-)	131 (53.7%)	126 (52.1%)	
Right colon (-transverse)	51 (20.9%)	48 (19.8%)	
Both	62 (25.4%)	68 (28.1%)	
Pathologic features			
Non-neoplastic	23 (8.4%)	28 (9.8%)	0.557
Neoplastic			
Dysplasia	184 (66.9%)	178 (62.2%)	0.269
HG dysplasia + CIS[1]	44 (16.0%)	51 (17.8%)	0.626
Cancer	24 (8.7%)	29 (10.2%)	0.557
Procedure related features			
Inexpert operator[2]	42 (17.2%)	48 (19.8%)	0.626
En bloc resection	261 (94.9%)	268 (93.7%)	0.070

[1]HG + CIS, high grade dysplasia + carcinoma *in situ*. [2]Inexpert operator, experience in polypectomy < 2 years.

was 56.6 ± 11.3 years, 379 men and 182 women were included in this study. There was no significant difference between the two groups in clinical features and base line characteristics, including the size, distribution, shape of the polyps and the pathological diagnosis (Table 1). The mean size of polyps was 14.5 mm ± 5.7 mm and 15.0 mm ± 6.8 mm in each group, and these polyps were usually present in the left colon (53.7% and 52.1% in each group). The protruding type of polyp was dominant, accounting for 74.5% and 72% in each group. Neoplastic polyps were present in 91.6% and 90.2% of each group, including coexisting cancer (8.7% and 10.2% in each group, respectively). The rate of *en bloc* polypectomy was high in both groups, accounting for 94.9% (261/275) and 93.7% (268/286) respectively.

Postpolypectomy bleeding

The overall rate of postpolypectomy bleeding (PPB) was 4.9% (12/244) in the epinephrine group and 10.3% (25/242) in the saline group. There was no statistical significance in the overall PPB between the two groups. Early PPB showed a tendency to be high in the saline group (4.5 % *vs* 8.7%, P = 0.065), but statistical difference was not proved. Late PPB did not exhibit a statistical difference in the two groups (0.4 % *vs* 1.7%, P = 0.154) (Table 2).

Table 2 Postpolypectomy bleeding, n (%)

	Epinephrine group (n = 244)	Normal saline group (n = 242)	P value
Early bleeding	11 (4.5)	21 (8.7)	0.065
Late bleeding	1 (0.4)	4 (1.7)	0.154

Table 3 Risk factors for postpolypectomy bleeding (multivariable analysis)

Risk factor	Adjusted odds ratio (95% CI)[1]	P
Size (> 2 cm)	1.07 (1.01, 1.14)	0.034
Injection (normal saline only)	1.31 (0.57, 2.99)	0.527
Pathology (neoplastic)	9.88 (1.26, 77.75)	0.029
Morphology (protruding type: Ip, Isp, Is)	0.59 (0.18, 1.95)	0.393
Inexpert operator (< 2 yr)	2.62 (0.98, 7.06)	0.056
Hospitalization (not hospitalized)	2.14 (0.57, 8.04)	0.261

[1]Adjusted odds ratios are calculated from a multivariate logistic regression model except for age, sex and procedure time.

Colonoscopic features of postpolypectomy bleeding

Colonoscopic features were not statistically different between the two groups. There was no statistical difference in the disrtibution of colon polyps and the presence of multiplicity, or the shape of the colon polyp (Table 1). PPB was significantly higher in the case of large sized (> 2 cm) polyps (Table 3).

Histologic and other features of postpolypectomy bleeding

PPB was significantly higher in neoplastic polyps, but there was no statistical significance in the pattern of neoplastic histology (dysplasia, high grade dysplasia or carcinoma *in situ*, cancer). The less experienced endoscopist (< 2 years) observed high PPB in nonhospitalized patients, but a statistical significance was not shown (Table 3). No free perforation was observed in relation to the procedure. In all the patients with postpolypectomy bleeding, endoscopic treatment was successfully performed without the need for surgery or angiography.

DISCUSSION

Several prospective studies have shown that removal of adenomatous polyps is associated with a reduction in the incidence of colorectal cancer[1,2]. Endoscopic polypectomy is a standard method of treatment of polyps in the gastrointestinal tract, but it is associated with substantial complications. Bleeding is the most frequent complication of endoscopic polypectomy. The reported incidence of bleeding after polypectomy ranges from 0.3% to 6.1%[1-5]. To reduce this complication, two aspects of technical development should be considered. One is the type of cutting currents used, such as a pure cutting current, blended current or pure coagulation. The other is the use

of a submucosal cushion injection.

The effect of pure cutting current is to vaporize the cells, whereas coagulation tends to heat-seal blood vessels[11]. Therefore, the risk and pattern of bleeding might be expected to differ depending on the type of currents used. Using a pure cutting or a blended current, the major episode was immediate hemorrhage, in contrast to delayed hemorrhage with a pure coagulation current[12]. Pure cutting current has several advantages over pure coagulation current because it is a faster procedure which provides clearer margins in the resected specimen and reduces the risk of transmural burn and perforation. However, it is generally accepted that if pure cutting current is used for polypectomy, hemostasis would be inadequate, and the risk of bleeding is high[4]. Therefore, the coagulation or blended electrosurgical current is generally preferred, because it is believed to reduce the risk of major hemorrhage. One survey of colonoscopic polypectomy practices among clinical gastroenterologists reported that the electrosurgical current used for polypectomy was pure coagulation current in 46%, blended current in 46%, and pure cutting current in 4%[6]. Because of the risk of transmural burn and delayed bleeding which is more difficult to treat than immediate bleeding, we theoretically believe that the blended current is safer and more effective than the pure coagulation current. In the present study, to preclude interprocedural bias, only one type of electrocoagulation or blended current, was used.

Submucosal saline injection has been demonstrated to be an effective method for a complete endoscopic polypectomy, especially in flat or sessile lesions[13,14]. Elevation of the colorectal polyp far enough from the muscle layer and serosal surface prevents a deep intramural burn as well as perforation[8]. Besides the prevention of perforation, the injection technique might also reduce the bleeding rate after polypectomy[9,14-16]. In one retrospective study[15], among 77 polyps more than 15 mm in diameter, there was no bleeding in the epinephrine injection group (28 polyps). In contrast, 9 of 49 polypectomies (18.4%) without submucosal injection were associated with a bleeding episode. There are 2 prospective studies on the efficacy of prophylactic submucosal saline-epinephrine injection in colonoscopic polypectomy[9,16]. A total of 120 patients with 151 sessile polyps were randomized into the epinephrine injection group or the control group. There was no significant difference in overall PPB, but immediate bleeding occurred significantly less frequently in the epinephrine group than in the control group (1/75 *vs* 7/76, $P = 0.03$)[9]. In another prospective study[16], 100 polyps (more than 10 mm in size) were randomized to receive submucosal injection or no injection, and there were nine episodes of PPB, one in the epinephrine group and eight in the control group (1/50 *vs* 8/50, $P < 0.05$). Although submucosal saline-epinephrine injection has been shown to reduce the risk of PPB, there is no prospective randomized study to compare PPB between submucosal saline injection with epinephrine and saline injection alone. Various submucosal injection materials, such as hyaluronic acid, fibrinogen mixtures and other viscoelastic substances, have been introduced into the conventional polypectomy and extended endoscopic mucosal resection, but these materials may have some side effects[17,18]. Submucosal injection of diluted epinephrine is a simple, effective, and cheap method for endoscopic polypectomy. The proposed method can affect tamponade, vasoconstriction, endarteritis, and possibly has a direct effect on the clotting process at the site of arterial defect. One major concern is the safety of epinephrine injection. However, side effects seem to be very rare in all aspects of therapeutic endoscopy, both epinephrine and mixed injection materials carry unwanted theoretical risks, such as local ischemia and cardiovascular side effects[19].

In the present study, the epinephrine injection did not show superiority over the saline injection in decreasing PPB. There was no statistical significance in overall and delayed PPB between the two groups. As in a prior study[9], early PPB showed a tendency to be high in the saline group (4.5 % *vs* 8.7%), but statistical difference was not proved. Although type-2 error could be influential, this result shows that there is no mandate to include epinephrine in injection fluid for conventional colonoscopic polypectomy.

Immediate bleeding can generally be treated successfully by endoscopic hemostasis. Some efforts have been made to decrease the delayed PPB using mechanical devices and many endoscopists prefer pretreatment of pedunculated polyps with thick stalks by placement of a detachable snare[20,21]. However, the clinical benefit may be marginally significant only for pedunculated polyps. Therefore, the use of detachable snares in clinical practice is not mandated. Another prospective trial showed that prophylactic clip placement does not decrease the occurrence of delayed PPB[22]. In the present study, there was no preventive method for delayed bleeding, and PPB was successfully controlled by endoscopic hemostasis without operation or angiographic embolization.

In general, the risk of PPB increases with the size of polyps and a more proximal colonic location. For polyps larger than 2 cm in diameter, particularly in the proximal colon, bleeding rate may exceed 10%[23,24]. In the present study, a multivariate logistic regression model excluding age, sex and procedure time showed that the size of polyp (> 2 cm) and neoplastic histology were associated with the risk of PPB ($P < 0.05$). In terms of large polyps, possible explanations for the increased risk are that resection of large polyps is technically more difficult, and these large lesions may contain large vessels. In terms of the neoplastic histology, it is difficult to interpret this finding, and to our knowledge, no study has shown such a result. There was no statistical difference in the site of colon polyp. Other possible causal factors for PPB include that the less experienced endoscopist (< 2 years) observed high PPB in nonhospitalized patients. However, these differences did not show a statistical significance.

The main limitation of our study was the relatively small sample size. Because the rate of PPB was less than 5%-10%, larger-scale studies are necessary to confirm our results. Another limitation was the method of polypectomy. Recently, for flat or depressed lesions greater than 20 mm in diameter, endoscopic mucosal resection with precutting or endoscopic submucosal dissection method has been recommended. It is presumed that complication rate due to more complex methods will be

different from that due to conventional snare polypectomy.

In conclusion, prophylactic submucosal injection of diluted epinephrine does not appear to offer a distinct advantage over saline injection for preventing postpolypectomy bleeding. Submucosal injection of normal saline is an adequate method for safe and effective colonoscopic polypectomy using the conventional snare method.

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