

**Risk Factors for Delayed post-EMR
Hemorrhage in Patients
with Gastric Neoplasms**

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Hemorrhage in Patients
with Gastric Neoplasms**

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ABSTRACT

Risk Factors for Delayed post-EMR Hemorrhage in Patients with Gastric Neoplasms

Background: Although endoscopic mucosal resection (EMR) has been recognized as the standard treatment for mucosal gastric neoplasm, post-EMR hemorrhage (PEH) remains a major complication of EMR, and this problem seems to be on the increase due to the development of invasive techniques. The aims of this study were to determine the incidence and grade of immediate or delayed PEH and to identify risk factors for delayed PEH in patients with gastric neoplasm.

Methods: Data of EMRs performed by three endoscopists were retrospectively collected over 8 years and then analyzed. The clinical records, the EMR and 24 hr follow-up endoscopic procedures were reviewed for 157 patients with gastric adenoma or early gastric cancer. Immediate PEH was defined as the bleeding during the procedure. Delayed PEH was defined when 2 of 4 following parameters were satisfied after the EMR period; 1) hematemesis, melena

or dizziness, 2) hemoglobin loss >2 g/dL, 3) blood pressure decrease >20 mmHg or pulse rate increase >20 /min, and 4) Forrest I or IIa-IIb on follow-up endoscopy. The patient-related, neoplasm-related and procedure-related variables were evaluated as potential risk factors for PEH.

Results: A total of 157 patients (mean age: 64, M:F = 44:113) were reviewed. Twenty-nine patients (18.5%) and thirteen patients (8.3%) presented with immediate and delayed PEH, respectively. Multivariate logistic regression analysis revealed that the patient's age (<65 years; OR 0.18 95%, CI 0.03-0.96), the size of lesion (>15 mm; OR 5.45, 95% CI 1.03-28.79), and the experience of the endoscopist (>5 years; OR 0.07, 95% CI 0.01-0.71) were significantly predictive variables for the delayed PEH. However, immediate PEH was not related to any of the studied variables.

Conclusions: Considering the higher risk of delayed PEH, careful preparation and close monitoring are required for elderly patients (>65 years), large sized gastric neoplasms (>15 mm), or EMR performed by an inexperienced endoscopist (≤5 years).

Key words; Risk factor, Endoscopic mucosal resection, Hemorrhage, Gastric neoplasm

Risk Factors for Delayed post-EMR Hemorrhage in Patients with Gastric Neoplasms

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I. INTRODUCTION

Endoscopic mucosal resection (EMR) has become a widely accepted therapeutic strategy for gastric mucosal neoplasm because it is a minimally invasive and highly effective procedure. In particular, EMR has come into the spotlight owing to improvements of the endoscopic devices that allow for early detection of small lesions.¹⁻⁵ Considering that it can be performed even in outpatients, EMR is minimally invasive and more beneficial in the aspect of cost-effectiveness when compared with surgical resection. EMR can provide long-term survival rates comparable to surgical therapy, provided that adherence to strict inclusion criteria is followed.⁶

Even if EMR's safety has been substantiated, unexpected complications can diminish the effectiveness of EMR in some patients. Complications of EMR include pain, hemorrhage, perforation and stricture formation. Of those, hemorrhage is the most common complication and it can cause a fatal outcome. In addition, post-EMR hemorrhage (PEH) seems to be increasing due to the generalization of invasive techniques such as endoscopic submucosal dissection. Whereas a previous study reported on the frequency of colonoscopic post-polypectomy bleeding,⁷ detailed studies concerning the risk factors for PEH in the stomach are scarce.⁸ In this study, we investigated the incidences of immediate and delayed PEH, and we evaluated the patient-related, gastric neoplasm-related and procedure-related factors that can predict the risk of developing delayed PEH in patients with gastric neoplasm.

II. PATIENTS AND METHODS

1. Patients

From January 1995 to June 2003, EMR was performed by three endoscopists on 157 patients with gastric neoplasm at the Yonsei University Wonju Christian Hospital, Gangwondo, South Korea. The 157 lesions consisted of 62 early gastric cancers and 95 gastric adenomas. The indication for EMR in patients with EGC included intramucosal differentiated adenocarcinoma without any ulceration or fibrosis being noted in the submucosal layer.

2. Preparations

EMR was performed using an endoscope (GIF-Q200, 240, 260, Olympus Optical Co., Ltd., Tokyo, Japan) under topical anesthesia of the pharynx and with intravenous injections of midazolam (0.05 mg/kg, Roche Korea Ltd.) and meperidine (0.5 mg/kg, Korea). After careful observation and confirmation of the lesion by dye spraying (0.2% indigocarmine), the margin of

the lesion to be resected was marked by a needle-knife using coagulation current (40W).

Normal saline solution with or without epinephrine (1:10,000) was injected into the submucosa to detach the lesion from the muscle layer and to prevent possible bleeding or perforation.

3. EMR methods

In the present study, we used two techniques of EMR, i.e. strip biopsy or ligation devices. The strip biopsy method was performed in 58 patients and EMR with the ligation (EMRL) method was performed in 99 patients. Strip biopsy was performed with a two-channel scope. A snare and grasping forceps were inserted via the accessory channel. The snare loop was opened in the stomach, and the grasping forceps was passed through the loop. The tissue adjoining the lesion was next grasped and lifted with the grasping forceps. The snare was opened and the lesion was then ensnared. Electrosurgical blended current (Valleylab generator, Boulder, Colo., USA), which was composed of coagulation (40W) and cutting (80W) current, was then applied to resect the lesion. The resected specimens were removed and then examined histopathologically. The EMRL method was performed via a frontal view electronic endoscope

equipped with a ligation device (the O-ring from the Stiegman-Goff endoscopic ligator kit, 12-mm outer diameter, 10.5-mm inner diameter, 10-mm depth; Bard International Inc., Tewksbury, MA, USA). The target lesion was aspirated into the O-type ligation device. The iatrogenic pseudopolypoid lesion was resected by snare polypectomy with high-frequency electrocauterization just below the ligation band. Because the maximal size of the specimen resected by EMRL is 1.5 cm, the size of neoplasm as an independent variable was determined by this criterion. After the EMR, endoscopy followed on day one after EMR.

4. Definitions of immediate and delayed PEH

Immediate PEH was defined as the bleeding that occurred during the procedure, and the grades of immediate PEH were classified as G1 (oozing, but not requiring endoscopic intervention), G2 (continued oozing requiring endoscopic intervention), and G3 (active spurting) (Figure 1). Delayed PEH was defined when 2 of 4 following parameters were satisfied after the EMR procedure; 1) hematemesis, melena or dizziness, 2) hemoglobin loss >2 g/dL, 3) a blood pressure decrease >20 mmHg or a pulse rate increase >20 /min, and 4) Forrest I, IIa-IIb on follow-up endoscopy.

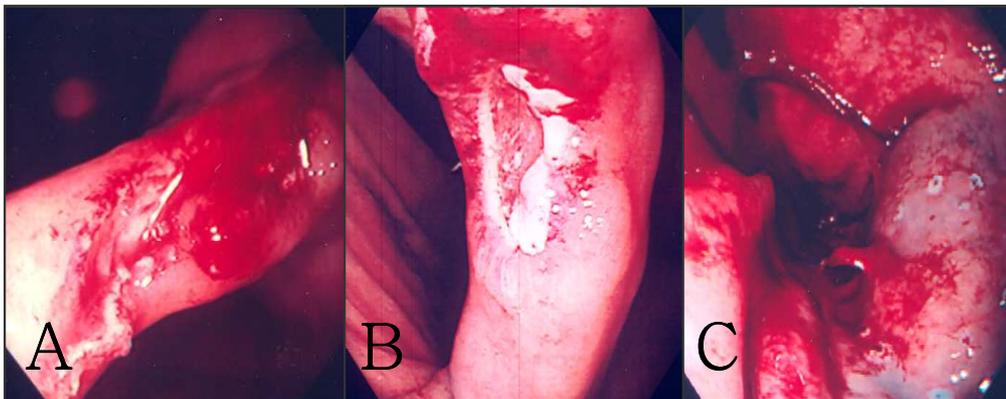


Figure 1. Degree of immediate PEH. A, Endoscopic view of grade I PEH; spontaneous hemostasis without endoscopic treatment. B, Endoscopic view of grade II PEH; oozing requiring endoscopic treatment. C, Endoscopic view of grade III PEH; active spurting

5. Variables

The patient-related variables (age, gender, presence of chronic disease, prior drugs such as aspirin, NSAID or warfarin use, and the American Society of Anaesthesiologists (ASA) physical status), the neoplasm-related variables (number, type, size, location, presence of *en bloc* resection, gross and microscopic characteristics), and the procedure-related variables (experience of the endoscopist, procedure time and type of electrosurgical current applied) were evaluated as potential risk factors for PEH. Complete blood count (CBC), prothrombin time (PT), and partial thromboplastin time (PTT) were measured before the procedure, and another CBC was done on the day after the procedure.

6. Statistical Analysis

All statistical tests were performed by two-sided tests and a p-value < 0.05 was considered statistically significant. Statistical analysis was performed with the SPSS PC window program (Statistical Package for the Social Science, SPSS Ins, Chicago, USA). Associations between the categorical predictors and delayed PEH were assessed by the chi-square test. Multiple logistic regression analysis for the risk factors of delayed PEH was performed to examine the effects of the independent variables, and adjustments were made for the effects of each of the variables on the other variables.

III. RESULTS

1. Characteristics of patients

A total of 157 patients (mean age: 64, M:F=44:113) were reviewed (Table 1). Fifty of the patients had chronic concomitant diseases and five patients had been using drugs related to bleeding tendencies. For the functional classification, 135 patients were ASA status 1, 20 patients were status 2, and 2 patients were status 3. Most of patients (151 of 157 patients, 96.2%) had one neoplasm at the time of the procedure. The removed lesions consisted of 62 EGCs and 95 adenomas.

Table 1. Characteristics of patients

Characteristics	Patients (n = 157)
Age (yr)	63.6 ± 9.8
Sex (F/M)	44/113
Past history of chronic disease	50 (31.8%)
Prior drug use related to hemorrhages	5 (12.4%)
ASA status (1/2/3)	135/20/2
Number of neoplasm (1/2/3)	151/3/3
Early gastric cancer / Adenoma	62/95

ASA, American society of anaesthesiologists

2. Characteristics of gastric neoplasms

The characteristics of the gastric neoplasms are shown in Table 2. The mean size of the lesions was 11 mm. The overall *en bloc* resection rate was 59% (92/157). The most common location was the antrum and greater curvature. Immediate PEH occurred in 29 of 157 patients (18.5%; 25 were G1, 3 were G2 and 1 was G3). In the majority of the cases, endoscopic intervention was not necessary due to spontaneous hemostasis. Three cases of G2 bleeding were easily controlled by application of a hemoclip and 1 case of G3 bleeding was controlled by local injection therapy. Delayed PEH occurred in 13 of 157 patients (8.4%). In all 17 cases, the bleeding was controlled by endoscopic hemostasis.

Table 2. Characteristics of gastric neoplasms

Characteristics	Neoplasms
Size of neoplasm (mm, range)	11.3 ± 5.7 (2-30)
Location of neoplasm (body/antrum)	22/ 135
Location of neoplasm (LC/GC/AW/PW)	41/ 65/ 26/ 25
Gross findings	
EGC (I/ IIa/ IIb/ IIc/ IIa+c/ IIc+a)	9/ 15/ 10/ 15/ 11/ 2
Adenoma (flat/ Yamada-I/ LST)	36/ 57/ 2
Microscopic findings	
EGC (W-D/ M-D)	38/ 24
Adenoma (LGD/ HGD/ Others)	62/ 12/ 21
<i>En bloc</i> / piecemeal	92/ 65

LC, lesser curvature; GC, greater curvature; AW, anterior wall; PW, posterior wall; LGD, low grade dysplasia; HGD, high grade dysplasia, W-D, well differentiated; M-D, moderate differentiated; LST, laterally spreading neoplasm

3. Univariate analysis of post-EMR hemorrhage according to variables

On univariate analysis, we analyzed age, anticoagulant medication, type of neoplasm, size of neoplasm, location of neoplasm, EMR method, *En bloc* resection, kind of injection solution, procedure time and EMR experience of the endoscopist. No significant variable for immediate or delayed PEH was found on the univariate analysis (Table 3). Among variables mentioned above, the type of injection solution (normal saline solution or epinephrine-mix solution) was not related to the immediate ($p = 0.155$) or delayed ($p = 0.519$) PEH. The EMR method including strip biopsy or EMRL also did not have an influence on the frequency of immediate ($p = 0.395$) or delayed ($p = 0.233$) PEH. However, age, location of neoplasm and experience of the endoscopist had marginal significance on delayed PEH.

Table 3. Univariate analysis of post-EMR hemorrhage according to variables

	Immediate (<i>p</i> -value)	Delayed (<i>p</i> -value)
Sex	1	0.758
Age (>65 vs. ≤65)	1	0.075
Past history of chronic disease	0.509	1.0
Drug history	0.230	1.0
ASA status	0.785	0.315
Type of neoplasm (cancer vs. adenoma)	1.0	1.0
Size of neoplasm (>15 mm)	0.603	0.250
Location of neoplasm (LC/GC/AW/PW)	0.481	0.076
Type of EMR (strip vs. EMRL)	0.395	0.233
<i>En bloc</i> resection	0.143	0.387
Injection (nss vs. epi.)	0.155	0.519
Endoscopist (≤5 yr of exp.)	0.280	0.062
Procedure time (>20 min)	0.113	0.759

EMRL, EMR with ligation; *exp*, experience; *nss*, normal saline solution

4. Multivariate analyses of immediate and delayed post-EMR

hemorrhage according to variables

On multivariate logistic regression analysis, the immediate PEH was not related to any of the studied variables. On the other hand, the patient's age (<65 years; OR 0.18, 95% C.I. 0.03-0.96), size of the lesion (>15 mm; OR 5.45, 95% CI 1.03-28.79), and EMR experience of the endoscopist (>5 years; OR 0.07, 95% CI 0.01-0.71) were significant predictive variables for the delayed PEH (Table 4).

Table 4. Multivariate analyses of immediate and delayed PEH according to variables

	Immediate Hemorrhage		Delayed Hemorrhage	
	OR (95% C.I.)	<i>p</i> Value	OR (95% C.I.)	<i>p</i> Value
Sex (M)	1.07 (0.42-2.76)	0.883	1.34 (0.33-5.48)	0.683
Age (<65)	0.92 (0.39-2.17)	0.853	0.18 (0.03-0.96)	0.044
Location (body/ antrum)	1.18 (0.78-1.78)	0.438	0.96 (0.50-1.85)	0.912
Type of EMR (strip/ EMRL)	1.08 (0.45-2.59)	0.872	2.09 (0.57-7.65)	0.264
Piecemeal EMR	1.66 (0.69-4.04)	0.261	1.03 (0.26-4.03)	0.970
Endoscopist (>5 yr of exp.)	0.56 (0.21-1.50)	0.248	0.07 (0.01-0.71)	0.024
Procedure time (>20 min)	1.82 (0.74-4.47)	0.192	0.55 (0.12-2.48)	0.437
Size of lesion (>15 mm)	1.29 (0.42-3.99)	0.657	5.45(1.03-28.79)	0.046

IV. DISCUSSION

On the grounds of its safety and effectiveness, EMR is acknowledged as an alternative technique to surgery for the complete resection of gastric mucosal neoplasm.¹⁻³ Nevertheless, various complications can accompany EMR and these can cause unexpected and unwanted results. In particular, post-EMR hemorrhage (PEH) is the most common complication and the incidence of PEH reported in the previous literature ranges from 1.4% to 22%.^{5,9,12-18} In this study, the frequency of overall (immediate and delayed) bleeding was 27% (42 of 157 patients), which was a little higher than the previous results.⁸ This discrepancy was probably related to whether a mild degree of hemorrhage was included into the immediate PEH data. On the contrary, the frequency of delayed PEH was 8.4% (13 of 157 patients), and this was not much different from the previous studies. Delayed PEH was defined by relatively objective parameters and these might be the preferable variables for comparing the results of different studies. Additionally, in the view of the clinician, most of immediate PEH can be easily treated by endoscopic hemostasis during the resection procedure, regardless of the severity. Ono et al.³ reported that even spurting hemorrhage could be controlled easily and successfully by

endoscopic treatment, which would obviate the need for blood transfusion. Also in this study, we made every effort to use hemostatic procedures whenever necessary during EMR because we considered the presence of immediate PEH to be a warning sign of delayed PEH. For this reason, all of the immediate PEHs in our study were completely controlled during the resection procedure, and there was no occurrence of delayed PEH among these cases. Unlike immediate PEH, delayed PEH can be easily overlooked due to the gradual onset of signs and symptoms, and this can cause unpredictable patient deterioration. Furthermore, because delayed hemorrhage can prolong the admission period,^{3,5,9-11} it is very important, in respect to clinical practice, to find out the risk factors for delayed PEH. Even though there have been some reports about the risk factors for overall (immediate and delayed) PEH, they failed to provide useful predictors for delayed PEH. Therefore, we evaluated the patient-related, tumor-related and procedure-related variables as the risk factors for delayed PEH.

There appears to be a recent increase in the rate of PEH for some reasons. The intention of complete resection may seduce the endoscopist to attempt to do a more extensive resection. It was reported that the risk of hemorrhage was increased when the size of the neoplasms was

over 15 mm¹⁹, and there has also been a report that contradicts this finding.²⁰ In cases of *en bloc* resection, it's been reported that the extensive EMR, which is a procedure prone to inadequate coagulation around the resection margin, raised the possibility of PEH.²² Okano et al.⁸ proposed that insufficient coagulation could be the cause of delayed bleeding. On the univariate analysis, the size of the neoplasm and *en bloc* resection did not have significant influence on the rate of overall (immediate and delayed) PEH. However, on multivariate analysis, the size of neoplasm (>15 mm) was a risk factor for delayed PEH. Accordingly, for patients with large neoplasms, every attention should be paid to the hemostasis during EMR, and a careful monitoring should be done after EMR.

Some reports have argued that the recently adopted equipment or techniques were responsible for the increase of PEH.^{15-18,22} As compared with the conventional methods (EMRL, EMRC), the up-to-date techniques using the insulated tip (IT)-knife or the hook-knife make for easy access to *en bloc* resection. Miyamoto et al.²² reported that the *en bloc* resection rate with the IT-knife was high even for large lesions, including those lesions over 30 mm. On the contrary, many endoscopists are not familiar with these new techniques and they tend to spend

more time on resection. In addition, the methods of submucosal dissection, which can resect an invasive lesion directly, are more likely to bring on a risk of vascular injury.⁴ Consequently, while the endoscopists have achieved more favorable results with the new techniques in regard to complete resection, the risk of PEH took a turn for the worse as a corollary. In the present study, there was no difference in the rate of PEH between the conventional methods, strip biopsy and the EMRL method. On multivariate analysis, the EMR performed by an inexperienced endoscopist was a significant risk factor for delayed PEH. Therefore, the endoscopist's skill was a significant determinant for delayed PEH and it was a more important factor than the EMR method.

Some authors have reported that the location of neoplasms could be implicated in PEH.^{15,23,24} There were some studies showing that bleeding occurred more frequently in the upper area of the stomach compared with the middle and lower areas. Hirao et al.²³ reported that the submucosal arteries of the upper third were larger than the arteries in the other areas, and they were stubby or thick upon histological examination. Also, there could be some difficulties for the approach of the endoscope and therefore, the rate of PEH can be different according to the

location of the neoplasms. In the present study, there was a marginal statistical significance for delayed PEH according to the location of the neoplasms. Probably, the reason is that the majorities of lesions in our study (135 of 157 lesions, 85.9%) were disproportionately located in the lower portion of the stomach. Also, this may be somewhat responsible to the difference of accessibility among locations, and accessibility was a bit easier at the greater curvature and anterior wall (91 of 157 patients, 57.9%).

Although it has recently become possible to perform a safe and effective procedure in the elderly with the help of supplementary oxygen and monitoring devices,²⁵ it is rather common knowledge that the general patient conditions such as age, the presence of comorbidities and functional status could be the major determinants of wound healing and rebleeding for EMR. Vogiagis et al.²⁶ proposed that aging could alter the cyclooxygenase activity and prostaglandin synthesis, and thereby compromise the healing of tissue. On multivariate analysis, an age over 65 was a significant risk factor for delayed PEH. So, we can recommend the endoscopist to pay more attention to the elderly via careful monitoring and follow-up. Furthermore, a prospective study under the meticulously controlled conditions would be helpful to examine this issue.

In conclusion, considering the higher risk of delayed PEH, careful preparation and close monitoring are required with elderly patients (>65 years), with a large sized gastric neoplasm (>15 mm), or when the the resection procedure is performed by an inexperienced endoscopist (≤ 5 years).

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국문요약

위 종양 환자의 내시경적 점막 절제술 후 지연 출혈 발생의 위험 인자

연세대학교 대학원

의학과

박동훈

배경: 내시경적 점막 절제술(Endoscopic mucosal resection, EMR)은 위 점막 종양의 주된 치료로 인정받고 있지만, 시술 후 출혈(Post-EMR hemorrhage, PEH)이 주요 합병증이며, 침습적인 시술방법이 개발되면서 발생 빈도가 증가하는 양상이다. 본 연구에서는 시술후의 조기 또는 지연 출혈의 빈도와 정도를 알아보고, 위종양이 있는 환자에서 지연 출혈의 발생에 관여하는 위험인자를 조사하였다.

방법: 1995년 1월부터 2003년 6월까지 세 명의 내시경 전문의에 의해 시행된 내시경적 점막 절제술의 자료를 후향적으로 분석하였다. 위선종이나 조기 위암이 있었던 157명의 환자에서 임상 기록과 내시경적 점막 절제술 소견, 그리고, 시술 24시간 후의 추적 내시경 검사 소견을 분석하였다. 시술 후 조기출혈은 시술중에 발생하는 출혈로 정의하였다. 지연 출혈은 시술 후에 다음의 네가지 조건 중 두가지 이상을

만족하는 경우로 정의하였다; 1) 토혈, 흑색변, 어지러움증이 있는 경우, 2) 혈색소 수치가 2 g/dL 이상 감소한 경우, 3) 혈압이 20 mmHg 이상 감소하거나, 맥박이 20/min 이상 증가한 경우, 4) 추적 내시경 소견상 Forrest I 이나 IIa-IIb 에 해당하는 경우. 시술 후 지연출혈의 위험인자를 알아보려고 환자, 종양, 그리고, 시술과 관련된 변수들을 조사하였다.

결과: 대상 환자의 평균 연령은 64세 였으며, 남자가 44명, 여자가 113명이었다. 조기 출혈은 29명(18.5%)의 환자에서, 지연 출혈은 13명(8.3%)의 환자에서 관찰되었다. 다변량 회귀 분석에서 환자의 나이(<65세; OR 0.18, 95% CI 0.03-0.96), 병변의 크기 (>15 mm; OR 5.45, 95% CI 1.03-28.79), 시술자의 경력(>5년; OR 0.07, 95% CI 0.01-0.71) 이 지연 출혈의 발생에 있어 의미 있는 위험인자였다. 그러나, 대상 변수들 중에서 조기출혈의 위험인자는 없었다.

결론: 지연출혈의 높은 위험성을 고려할 때, 환자의 나이가 65세 이상일 경우나, 병변의 크기가 15 mm 이상일 경우, 시술자의 경험이 5년 이하일 경우에는 보다 주의 깊은 사전준비와 철저한 환자감시가 요구된다.

핵심 되는 말; 위험인자, 내시경적 집막 절제술, 출혈, 위종양