Modified coagulation and clipping method for the prevention of post-operative bleeding after gastric endoscopic submucosal dissection: A multicenter propensity score matching analysis

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Abstract. The prevention of post-operative bleeding is currently a critical issue associated with endoscopic submucosal dissection (ESD), where combined anti-thrombotic therapy is the standard in a super-aged society. Post-ESD coagulation (PEC) is widely performed to prevent post-operative bleeding; nonetheless, post-operative bleeding rates associated with gastric ESD continue to be reported in 3.1-5.5% of cases. The present study aimed to examine the effectiveness of a novel technique, the modified coagulation and clipping (MCC) method, in preventing post-operative bleeding associated with ESD. Overall, 481 patients were treated between April, 2007 and July, 2020. Between July, 2010 and June, 2020, the MCC method was adopted. The incidence of post-operative bleeding was assessed following gastric ESD and the clinical conditions affecting post-operative bleeding during this period were analyzed retrospectively. In addition, the incidence of post-operative bleeding associated with gastric ESD and the clinical conditions in the 3-year period from April, 2007 to June, 2010 were assessed, during which PEC was employed, as a historical control. The bleeding rates for these two periods were compared using propensity score matching (PSM). Of the 481 included patients, 160 and 321 patients underwent the PEC and MCC method, respectively. In total, 9 patients (5.6%) in the PEC group developed post-operative bleeding, whereas no patient (0.0%) in the MCC group developed post-operative bleeding. The PSM analysis revealed that the MCC method was significantly associated with the prevention of post-operative bleeding. On the whole, the findings of the present study indicate that the MCC method is a promising technique for preventing post-operative bleeding associated with ESD. However, further studies are required to identify the optimal indications.

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Abbreviations: 2C, coagulation plus artery-selective clipping; ESD, endoscopic submucosal dissection; JGES, Japan Gastroenterological Endoscopy Society; MCC, modified coagulation and clipping; PEC, post-ESD coagulation; PSM, propensity score matching

Key words: endoscopic submucosal dissection, post-operative bleeding, coagulation and clipping, propensity score matching

Introduction

Endoscopic submucosal dissection (ESD) is a minimally invasive treatment used to achieve the curative resection of early-stage gastric cancer with almost no risk of lymph node metastasis (1-5). However, ESD continues to be associated with procedure-related adverse events. In particular, post-operative bleeding is a major adverse event associated with ESD. Post-operative bleeding, once it occurs, can be a severe medical condition, requiring blood transfusion or resulting in shock. It also prolongs hospital stays and has a significant negative effect on the quality of life of patients and healthcare economics. Therefore, it is a contingency that should be prevented as far as possible.

In Japan, the publication of the Japan Gastroenterological Endoscopy Society (JGES) guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment (6) has led to more opportunities for ESD with continued anti-thrombotic therapy. The management of post-operative

bleeding is therefore an increasingly critical clinical issue associated with the use of ESD.

Hemostatic procedures, such as post-ESD coagulation (PEC) (7), are performed for post-ESD ulcers to prevent post-operative bleeding, which occurs in 3.1-5.5% of cases (7-9). Mukai *et al* (10) and Azumi *et al* (11) reported the usefulness of coagulation plus artery-selective clipping (2C) and search, coagulation and clipping (SCC), respectively. These procedures reduced the post-operative bleeding rate compared with the use of PEC alone (10,11). The present study further modified this method of coagulation and clipping to reduce the risk of post-operative bleeding. This approach requires the coagulation of arteries and residual vessels at the margin of the ESD ulcer. Additional clipping involving the muscular layers was performed to provide additional strength and prevent delayed perforation due to over-coagulation. This modified coagulation and clipping (MCC) method was termed the 'MCC method'.

The aim of the present retrospective study was to evaluate the effectiveness of the MCC method in preventing post-operative bleeding associated with ESD, and in addition, to compare its usefulness with conventional hemostatic methods.

Patients and methods

Patients. Patients >18 years of age who underwent gastric ESD for gastric cancer at Fukuchiyama City Hospital (Fukuchiyama, Japan), Kyoto Kujo Hospital (Kyoto, Japan) and Saiseikai Suita Hospital (Suita, Japan) between April, 2007 and July, 2020 were enrolled in the present study. In patients who underwent ESD for two or more lesions simultaneously, the largest lesion was selected as the representative lesion. Patients with a history of esophagectomy or gastrectomy were excluded from the study. The protocol for the present study was approved by the Clinical Ethics Committees on Human Experiments of Fukuchiyama City Hospital (IRB registration no. 4-7), Kujo Hospital (IRB registration no. H291213) and Saiseikai Suita Hospital (IRB registration no. 2020-12), and it conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). Written informed consent was obtained from all patients prior to their participation in the study.

Patient characteristics. Patients medical records were reviewed and the following data were collected: Age, sex, use of anti-thrombotic agents, tumor location, tumor size, resected specimen size, histology, invasion depth, the presence of ulcerations, duration of surgery, number of clips used, time of clipping and ESD-related complications.

Study design. Between July, 2010 and June, 2020, the MCC method was introduced and performed in 321 patients undergoing ESD. The incidence of post-operative bleeding was assessed following gastric ESD and the clinical conditions affecting post-operative bleeding during this period were also assessed. In addition, the incidence of post-operative bleeding following gastric ESD and the clinical conditions in the 3-year PEC period from April, 2007 to June, 2010 were assessed as a historical control. The bleeding rates were compared between the PEC period and MCC period.

ESD procedure and management following ESD. Gastric ESD was performed with an insulated-tip knife-2 (KD-611L, Olympus Corporation), a Flush knife (DK2620J; FUJIFILM Wako Pure Chemical Corporation) and a clutch cutter (DP2618DT; FUJIFILM Wako Pure Chemical Corporation) through a conventional single-channel endoscope (EG-580RD, FUJIFILM Wako Pure Chemical Corporation; and Q260J, Olympus Corporation). Marker dots were made ~5 mm from the lesion. Following the submucosal injection of hyaluronic acid, a circumferential mucosal incision was made outside the marked region. Submucosal dissection was performed in all cases. The hemostasis of active bleeding and the preventive of coagulation of all visible vessels were performed during or following ESD using hemostatic forceps (FD-411QR; Coagrasper, Olympus Corporation) or hot biopsy forceps (HOYA Corporation,PENTAX Lifecare Division).

A proton-pump inhibitor was intravenously injected twice daily from the day prior to ESD to the day following ESD. The patients were supplied with drinking water 2 h following ESD. A second-look endoscopy was performed the following day. Liquid food was also provided with no complications. Oral proton-pump inhibitors were administered from 2 days following ESD to 8 weeks thereafter.

Participating endoscopists. From April, 2007 to June, 2010, three endoscopists performed ESD. They had experience with >50 gastric ESDs. From July, 2010 and June, 2020, eight endoscopists performed the ESDs. They had experience with >100 gastric ESDs.

Management of anti-thrombotic agents. For patients receiving oral anti-thrombotic agents, such as low-dose aspirin, thienopyridine, cilostazol, warfarin, dabigatran, rivaroxaban, apixaban and edoxaban, the prescribing doctor was consulted regarding the management of anti-thrombotic agents prior to ESD. Prior to the publication of the JGES guidelines for gastroenterological endoscopy in patients undergoing anti-thrombotic treatment (6), anti-thrombotic agents were almost always discontinued prior to ESD. Following the publication of the JGES guidelines, the management of anti-thrombotic agents was determined according to the guidelines. The discontinued period of anti-thrombotic agents prior to the ESD procedure was as follows: Aspirin, thienopyridine, cilostazol, warfarin and direct oral anticoagulants were withdrawn at 3-5, 5-7, 2, 3-4 and 1 day prior to ESD, respectively.

MCC method. For patients undergoing the MCC method, the operator or assistant recorded the location of the blood vessels that caused intraoperative bleeding and required hemostasis with hemostatic forceps or in which preventive coagulation with hemostatic forceps was performed.

Following the ESD procedure, additional coagulation was performed at the sites where the location was recorded, at the penetrating blood vessels in the muscular layer and at the margin of the ESD ulcer. Additional hemostatic clips (HX-610-135; Olympus Corporation) were applied to include the muscular layer for the additional strength of the vessels and to prevent delayed perforation owing to over-coagulation (Figs. 1 and 2).

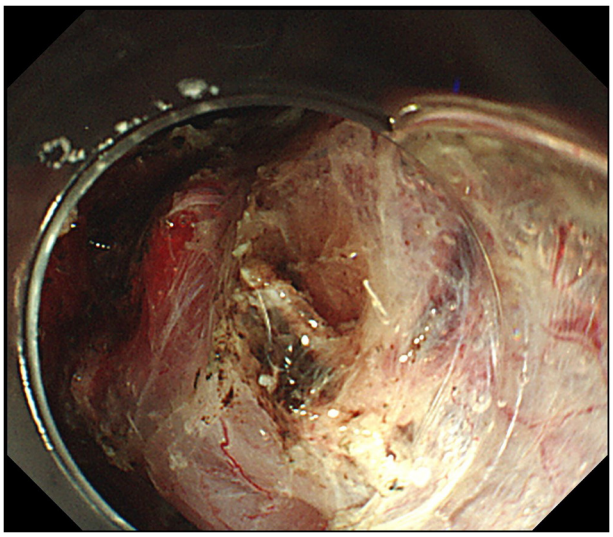

Figure 1. Image illustrating that the blood vessel with pulsation was detected. Thus, coagulation using hemostatic forceps was performed, and hemostatic clips were applied.

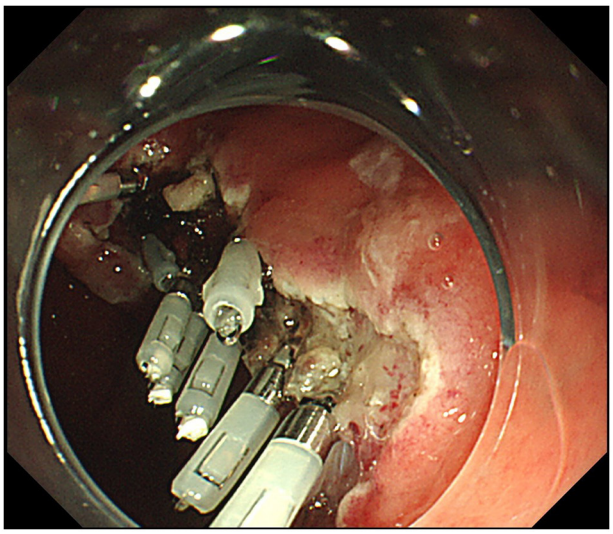

Figure 2. Image illustrating that post-endoscopic submucosal dissection ulcer after the modified coagulation and clipping method was performed.

Definition of post-operative bleeding. Post-operative bleeding was defined as an event requiring urgent endoscopic hemostasis within 1 month following gastric ESD, such as hematemesis, melena or a decrease in the hemoglobin concentration by >2 g/dl. Endoscopic hemostasis was performed when active bleeding or blood coagulation was observed. Preventive hemostasis of visible vessels without bleeding was not regarded as post-operative bleeding.

Statistical analysis. For descriptive statistics, continuous variables are presented as the mean ± standard deviation or median, whereas discrete variables are presented as the frequency and proportion. For statistical analyses, the paired Student's t-test or Wilcoxon signed-rank test were used for discrete variables. The bleeding rates in the MCC and PEC groups were examined using odds ratios. When the event occurrence was 0, the continuity correction was conducted according to the Cornfield formula described in the study by Schlesselman (12). A two-sided P-value <0.05 was considered to indicate a statistically significant difference.

Table I. Clinical characteristics of all the patients in the present study and gastric lesions.

Variable	All patients (n=481)
Sex (male/female), n (%)	349/132 (72.6/27.4)
Age (mean ± SD) (years)	71.1±10.0
Antithrombotic agent, n (%)	89 (18.5)
Tumor location, n (%)	
Upper third of the stomach	74 (15.4)
Middle third of the stomach	133 (27.7)
Lower third of the stomach	274 (56.9)
Tumor size (mean ± SD) (mm)	14.7±10.3
Resected specimen size (mean ± SD) (mm)	35.9±12.7
Histological type of the tumor, n (%)	
Differentiated	465 (96.7)
Undifferentiated	16 (3.3)
Invasion depth, n (%)	
T1a	438 (91.1)
T1b or greater	43 (8.9)
Presence of ulceration, n (%)	37 (7.7)
Duration of surgery time (mean ± SD) (min)	75.7±72.9

SD, standard deviation.

Propensity score matching (PSM) was performed in order to adjust for confounding variables, where possible to reduce background differences due to differences in the period of treatment indication. The scores were calculated as the log-odds obtained by the logistic regression model, with response variables including the PEC or MCC groups. Explanatory variables consisted of tumor location, tumor size, resected specimen size, invasion depth, histological types, use of anti-thrombotic agents, and procedure time. Matching was performed using a 1:1 matching protocol with nearest-neighbor matching within a caliper width of 0.01 without replacement. The receiver operating characteristic and area under the curve were used to measure the balance of covariates. The matched datasets were examined for balance in terms of an absolute standardized difference. The propensity score was rounded from three to two decimal places. Matching was performed using three decimal places for the PEC and MCC groups.

Following PSM, the post-operative bleeding rates between the PEC and MCC groups were compared.

Statistical analyses were performed using STATA version 12.1 (StataCorp LP) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), R version 2.13.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Table II. Clinicopathological characteristics of the patients in the PEC and MCC groups.

Variable	PEC group (n=160)	MCC group (n=321)	P-value
Sex (male/female), n (%)	123/37 (76.9/23.1)	226/95 (70.4/29.6)	0.159
Age (mean ± SD) (years)	70.1±10.2	71.3±9.9	0.859
Antithrombotic agent, n (%)	25 (15.6)	64 (19.9)	0.264
Heparin replacement therapy, n (%)	8 (5.0)	9 (2.8)	0.222
Tumor location, n (%)			0.404
Upper third of the stomach	29 (18.0)	45 (14.0)	
Middle third of the stomach	46 (28.7)	87 (27.1)	
Lower third of the stomach	85 (53.1)	189 (58.9)	
Tumor size (mean ± SD) (mm)	15.7±9.8	14.2±10.5	0.034
Resected specimen size (mean ± SD) (mm)	37.8±13.0	34.9±12.4	0.019
Histological type of the tumors, n (%)			0.103
Differentiated	158 (98.8)	307 (95.6)	
Undifferentiated	2 (1.2)	14 (4.4)	
Invasion depth, n (%)			0.127
T1a	141 (88.1)	297 (92.5)	
T1b or greater	19 (11.9)	24 (7.5)	
Presence of ulceration, n (%)	12 (7.5)	25 (7.8)	0.999
Operation time median (range) (min)	101.6±100.1	62.8±49.8	<0.001
Number of clips (mean ± SD)	0	7.9±4.4	
Time of clipping (mean ± SD)	0	13.5±9.2	
Delayed perforation, n (%)	2 (1.3)	0 (0)	0.110
Post-operative bleeding, n (%)	9 (5.6)	0 (0)	<0.001

Data were analyzed using a Student's t-test (unpaired) or the Wilcoxon rank-sum test for continuous variables. Fisher's exact test was used for the discrete variables. The bleeding rates in the MCC and PEC groups were examined using odds ratios. When the event occurrence was 0, the continuity correction was conducted according to the Cornfield formula described in the study by Schlesselman (11). MCC, modified coagulation and clipping; PEC, post-endoscopic submucosal dissection coagulation; SD, standard deviation.

Results

A total of 481 (349 males and 132 females) patients were enrolled in the present study. The clinicopathological characteristics of these patients are summarized in Table I. The mean age was 71.1±10.0 years.

Out of the 481 patients, 321 underwent MCC and 160 underwent PEC, respectively. The clinicopathological characteristics of the groups are presented in Table II. Significant differences between the two groups were found in tumor size (P=0.034), resected specimen size (P=0.019), the duration of surgery (P<0.001) and post-operative bleeding (P<0.001). In total, nine patients developed postoperative bleeding; however, all of these patients were in the PEC group, with no patient in the MCC group. All cases of postoperative bleeding were successfully treated by endoscopic hemostasis. No major hemorrhaging occurred. In total, 2 cases of delayed perforation occurred in the PEC group, but not in the MCC group (Table II). The 2 cases of delayed perforation were endoscopically closed with clips.

Out of the 481 patients, 89 (18.5%) were on anti-thrombotic therapy for their comorbidities. The proportion of patients in each treatment group on anti-thrombotic therapy was 19.9% (64/321) in the MCC group and 15.6% (25/160) in the PEC group. Post-operative bleeding occurred in 0% (0/64) of the patients in the MCC group and in 4% (1/25) of the patients in the PEC group. No significant difference was observed between the two groups (P=0.281), although the incidence of post-operative bleeding was lower in the MCC group than in the PEC group (Table III).

Propensity score matching was used to create matched pairs of the MCC method and PEC method, and comparisons were made between matched pairs. Following PSM, there were 143 matched pairs of patients between the two groups. The details of the propensity score-matched patients are presented in Table IV. A significant difference in post-operative bleeding was identified between the two groups (P=0.004).

Discussion

The present study introduced the MCC method and confirmed its efficacy in preventing post-operative bleeding associated with gastric ESD, with good results: Not a single case of post-operative bleeding was observed in a multicenter setting over a 10-year period.

Post-operative bleeding associated with gastric ESD requires invasive intervention and, to date, has been difficult to eliminate. Mukai *et al* (10) and Azumi *et al* (11) reported

Table III. Clinicopathological characteristics of the patients on anti-thrombotic therapy in the PEC and MCC groups.

Characteristic	PEC group (n=25)	MCC group (n=64)	P-value
Post-operative bleeding, n (%)	1 (4)	0 (0)	0.281
Anti-thrombotic agent, n (%)			
Single antiplatelet agent	16 (64)	46 (71.8)	0.197
Dual antiplatelet agents	2 (8)	4 (6.3)	0.999
Anticoagulant agents	7 (28)	14 (21.9)	0.999
Heparin replacement therapy, n (%)	8 (32)	9 (14.1)	0.293

Data were analyzed using Fisher's exact test was used for discrete variables. The bleeding rates in the MCC and PEC groups were examined using odds ratios. When the event occurrence was 0, the continuity correction was conducted according to the Cornfield formula described in the study by Schlesselman (11). MCC, modified coagulation and clipping; PEC, post-endoscopic submucosal dissection coagulation.

Table IV. Clinicopathological characteristics of the patients in the PEC and MCC groups following propensity score matching.

	Following propensity score matching (n=286)			
Variable	PEC method (n=143)	MCC method (n=143)	ASD	P-value
Sex (male/female), n (%)	109/34 (76.2/23.8)	100/43 (69.9/30.1)	0.14	0.286
Age (mean ± SD), years	71.6±9.6	71.9±9.5	0.03	0.686
Anti-thrombotic agent, n (%)	23 (16.1)	26 (18.2)	0.05	0.754
Heparin replacement therapy, n	8	4		0.380
Tumor location, n (%)			0.00	0.683
Upper third of the stomach	23 (16.1)	19 (13.3)		
Middle third of the stomach	41 (28.7)	47 (32.9)		
Lower third of the stomach	79 (55.2)	77 (53.8)		
Tumor size (mean ± SD), mm	15.1±9.6	15.6±12.1	0.04	0.716
Resected specimen size (mean ± SD), mm	36.4±12.4	36.2±12.8	0.02	0.870
Histological type of the tumors, n (%)			0.14	0.498
Differentiated	141 (98.6)	143 (100)		
Undifferentiated	2 (1.4)	0 (0)		
Invasion depth, n (%)			0.13	0.441
T1a	133 (93.0)	137 (95.8)		
T1b or greater	10 (7.0)	6 (4.2)		
Presence of ulceration, n (%)	11	16		0.419
Duration of surgery, median (range) (min)	78.1±66.1	77.2±64.3	0.01	0.908
Number of clips (mean ± SD)	0	8.6±4.4		
Time of clipping (mean ± SD)	0	14.3±9.3		
Delayed perforation, n (%)	2 (1.4)	0 (0)		0.500
Postoperative bleeding, n (%)	8 (5.6)	0 (0)		0.004

Data were analyzed using a paired t-test or the Wilcoxon signed-rank test for continuous variables. Fisher's exact test was used for the discrete variables. The bleeding rates in the MCC and PEC groups were examined using odds ratios. When the event occurrence was 0, the continuity correction was conducted according to the Cornfield formula described in the study by Schlesselman (11). MCC, modified coagulation and clipping; PEC, post-endoscopic submucosal dissection coagulation; SD, standard deviation; ASD, absolute standardized difference.

that the 2C and SCC methods, respectively, reduced the post-operative bleeding rate compared with PEC alone. In the present study, no patient in the MCC group developed post-operative bleeding associated with gastric ESD. There

were no complications associated with the MCC method. On the other hand, 9 patients developed post-operative bleeding in the PEC group. In many of these cases, sufficient coagulation to the deeper layer of the muscle may not be achieved. This may cause post-operative bleeding.

The main difference between the MCC method and the other two clipping methods is the application of coagulation and clipping. The 2C and SCC methods coagulate vessels and clip for additional strength. By contrast, the MCC method coagulates vessels and applies clips not only to provide additional strength, but also to prevent delayed perforation due to over-coagulation. After the high-risk vessels and residual vessels at the margin of the ESD ulcer were coagulated, additional clipping involving the muscular layers surrounding the vessels was performed with sufficient clips. Accordingly, more clips are used in the MCC method (mean, 7.9 clips) than in either of the other two methods (mean, 3.8-4.8 clips). These factors may aid in preventing post-operative bleeding associated with gastric ESD. In the PEC group, 2 cases of delayed perforation occurred, but none in the MCC group. In the PEC group, vessels were coagulated sufficiently to prevent post-operative bleeding, although this may lead to over-coagulation, resulting in delayed perforation. No statistically significant differences between the PEC group and MCC group were identified due to the small number of cases of delayed perforation.

In the hyper-aged society of Japan, the number of patients undergoing ESD and receiving anti-thrombotic therapy is significantly increasing. In addition, the JGES guidelines for gastroenterological endoscopy in patients undergoing anti-thrombotic treatment (6) have made it commonplace to perform ESD with continued antithrombotic therapy. On the other hand, anti-thrombotic therapy is a definite risk factor for post-operative bleeding, particularly in patients receiving dual antiplatelet agents and heparin replacement therapy (13-17).

In the PEC implementation period between 2007 and 2010, anti-thrombotic drugs were withdrawn during ESD in the majority of cases, whereas after the guidelines were published in 2012, in the MCC implementation period between 2010 and 2020, the majority of patients continued their anti-thrombotic therapy or underwent heparin replacement intraoperatively according to the guidelines. Nevertheless, during the MCC introduction period, post-operative bleeding was successfully prevented in all cases (100%). These findings suggest that the MCC method is useful in preventing post-operative bleeding in patients receiving anti-thrombotic therapy.

From an economic point of view, one hemostatic clip costs 7.5 USD/825 JPY. Mukai *et al* (10) and Azumi *et al* (11) reported that 3.8 and 4.9 clips were required on average, respectively. In the present study, 7.9 clips were used on average. Thus, the cost was 59.2 USD/6,517.5 JPY. Considering that the incidence of post-operative bleeding is ~5%, it may be considered excessive to perform the MCC method for all patients undergoing gastric ESD. On the other hand, the cost is considered to be worth the benefit in cases with a high risk of bleeding with concomitant anti-thrombotic therapy and for the prevention of severe conditions and mortality in elderly patients who are vulnerable due to underlying diseases.

The present study had certain limitations which should be mentioned. First, the present study was conducted in three institutions with a limited number of patients. Second, the present study was a retrospective study, and was not conducted with a simultaneous control. Therefore, there was selection bias. It is not easy to estimate the effects of the MCC method alone, as advancements in devices and principles, and improvements in antacids may also have an impact on reducing the risk of post-operative bleeding. Intraoperative bleeding is slightly higher with an insulated-tip knife-2 and Flush knife than with a clutch cutter in ESD. Intraoperative bleeding may affect post-operative bleeding. Third, a longer enrollment period and significant differences in terms of tumor size, resected specimen size and duration of surgery between the PEC and MCC groups are further limitations. Significant differences in the duration of surgery between the two groups are due an improvement of technical skills with time. The propensity score We was calculated, matched pairs were constructed and these effects were equalized as much as possible. Comparisons on this basis also indicated that the MCC method was superior to the PEC method in preventing bleeding.

The prevention of bleeding is of utmost importance in very elderly individuals on anti-thrombotic therapy, whose general health is fragile and they have underlying diseases, and are thus at a risk of developing life-threatening subsequent bleeding. Furthermore, the healthcare costs of dealing with this phenomena can be exorbitant. The MCC method would be beneficial, particularly for these high-risk patients undergoing ESD, as no post-operative bleeding was observed in the present study.

To determine the size of the bleeding prevention effect of the MCC method alone, it is necessary to assess the effect size of the MCC method separately from the impact of advancements in ESD devices and antacid performance on bleeding prevention. For this purpose, evaluation using randomized control trials is desirable. Moreover, with the post-bleeding rate of <5% observed herein, which is not very high, a highly validated cost-effectiveness analysis that rigorously evaluates cost and effectiveness needs to be conducted to determine which subjects should be indicated for the MCC method.

In conclusion, the present study introduced a novel hemostatic prophylaxis technique termed the MCC method and the results are noteworthy: No post-operative bleeding was observed in a multicenter 10-year period. The MCC method was thus suggested to be a reliable bleeding prevention technique in ESD in the era of concomitant anti-coagulant therapy and in very elderly patients. Randomized controlled trials are required however, to fully clarify the role of the MCC method in the prevention of post-ESD bleeding.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KT performed the research, analyzed the data and wrote the manuscript. KO designed the study. KS analyzed the data. All the other authors (TaS, SA, TN, TM, NI, SF, HO, TK, KM, TOkuda, JM, YM, CM, MM, SM, ToS, YI and TOkanoue) contributed to the collection and interpretation of data for the study, and critically reviewed the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KT and KS confirmed the authenticity of all the raw data.

Ethics approval and consent to participate

The protocol for the present study was approved by the Clinical Ethics Committees on Human Experiments of Fukuchiyama City Hospital (IRB registration no. 4-7), Kujo Hospital (IRB registration no. H291213) and Saiseikai Suita Hospital (IRB registration no. 2020-12), and it conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). Written informed consent and patient consent for publication were obtained from all patients in the present study.

Patient consent for publication

Written informed consent was obtained from all patients in the present study for the publication of their data and any related images.

Competing interests

The authors declare that they have no competing interests.

References

1. Abe N, Yamaguchi Y, Takeuchi H, Izumisato Y, Yanagida O, Masaki T, Mori T, Sugiyama N and Atomi Y: Key factors for successful en bloc endoscopic submucosal dissection of early stage gastric cancer using an insulation-tipped diathermic knife. Hepatogastroenterology 53: 639-642, 2006.
2. Gotoda T: Endoscopic resection of early gastric cancer. Gastric Cancer 10: 1-11, 2007.
3. Kim BJ, Chang TH, Kim JJ, Min BH, Lee JH, Son HJ, Rhee PL, Rhee JC, Kim KM and Park CK: Efficacy and safety of endoscopic submucosal dissection for early gastric cancer in patients with comorbid diseases. Gut Liver 4: 186-191, 2010.
4. Oda I, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, *et al*: A multicenter retrospective study of endoscopic resection for early gastric cancer. Gastric Cancer 9: 262-270, 2006.
5. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T and Yoshida S: Endoscopic mucosal resection for treatment of early gastric cancer. Gut 48: 225-229, 2001.
6. Fujimoto K, Fujishiro M, Kato M, Higuchi K, Iwakiri R, Sakamoto C, Uchiyama S, Kashiwagi A, Ogawa H, Murakami K, *et al*: Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. Dig Endosc 26: 1-14, 2014.
7. Takizawa K, Oda I, Gotoda T, Yokoi C, Matsuda T, Saito Y, Saito D and Ono H: Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection-An analysis of risk factors. Endoscopy 40: 179-183, 2008.
8. Oda I, Suzuki H, Nonaka S and Yoshinaga S: Complications of gastric endoscopic submucosal dissection. Dig Endosc 25 (Suppl 1): S71-S78, 2013.
9. Okada K, Yamamoto Y, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Chino A, Tsuchida T, Fujisaki J, *et al:* Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. Surg Endosc 25: 98-107, 2011.
10. Mukai S, Cho S, Nakamura S, Hatano Y, Kotachi T, Shimizu A, Matsuura G, Azakami T, Takaba A, Hamada T, *et al:* Postprocedural combined treatment using the coagulation plus artery-selective clipping (2C) method for the prevention of delayed bleeding after ESD. Surg Endosc 27: 1292-1301, 2013.
11. Azumi M, Takeuchi M, Koseki Y, Kumagai M, Kobayashi Y, Takatsuna M, Yoshioka A, Yoshikawa S, Miura T and Terai S: The search, coagulation, and clipping (SCC) method prevents delayed bleeding after gastric endoscopic submucosal dissection. Gastric Cancer 22: 567-575, 2019.
12. James J, Schlesselman: Case control studies: Design, conduct, analysis (Monographs in Epidemiology and Biostatistics), January 21, 1982.
13. Terasaki K, Dohi O, Naito Y, Azuma Y, Ishida T, Kitae H, Matsumura S, Ogita K, Takayama S, Mizuno N, *et al:* Effects of guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment on postoperative bleeding after endoscopic submucosal dissection for early gastric cancer: A propensity score-matching analysis. Digestion 102: 256-264, 2021.
14. Shindo Y, Matsumoto S, Miyatani H, Yoshida Y and Mashima H: Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithrombotics. World J Gastrointest Endosc 8: 349-356, 2016.
15. Sanomura Y, Oka S, Tanaka S, Yorita N, Kuroki K, Kurihara M, Mizumoto T, Yoshifuku Y and Chayama K: Taking warfarin with heparin replacement and direct oral anticoagulant is a risk factor for bleeding after endoscopic submucosal dissection for early gastric cancer. Digestion 97: 240-249, 2018.
16. Igarashi K, Takizawa K, Kakushima N, Tanaka M, Kawata N, Yoshida M, Ito S, Imai K, Hotta K, Ishiwatari H, *et al*: Should antithrombotic therapy be stopped in patients undergoing gastric endoscopic submucosal dissection? Surg Endosc 31: 1746-1753 2017.
17. Furuhata T, Kaise M, Hoteya S, Iizuka T, Yamada A, Nomura K, Kuribayashi Y, Kikuchi D, Matsui A, Ogawa O, *et al*: Postoperative bleeding after gastric endoscopic submucosal dissection in patients receiving antithrombotic therapy. Gastric Cancer 20: 207-214, 2017.