



The use of diluted epinephrine during gastric endoscopic submucosal dissection: an international randomized controlled trial

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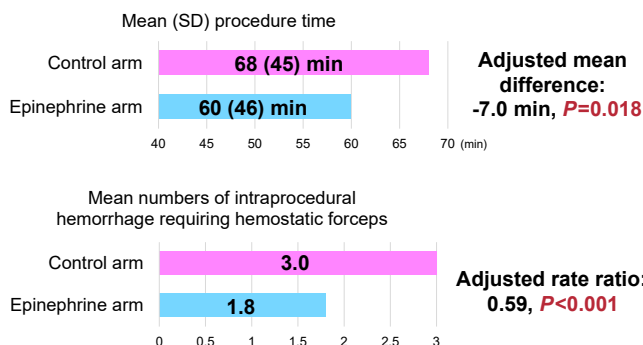
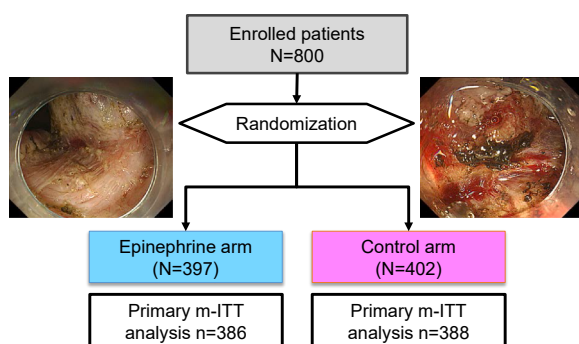
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GRAPHICAL ABSTRACT

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Background:

- Bleeding during gastric ESD often leads to unclear dissection view and a prolonged procedural time. Vasoconstrictive effect of epinephrine could potentially help reduce such bleeding and is recommended during resection of large pedunculated colon polyp.
- We conducted an international multicenter double blinded RCT to evaluate the effect of diluted epinephrine in the submucosal lifting solution during gastric ESD.



Conclusion

- The addition of diluted epinephrine (1:100,000) to a submucosal injection solution during gastric ESD shortened the procedure time and reduced intraprocedural bleeding requiring hemostatic forceps.
- This technique can be recommended as a routine practice for patients undergoing gastric ESD.

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Background and Aims: Endoscopic submucosal dissection (ESD) is the standard treatment for early gastric cancer. Intraprocedural bleeding during gastric ESD may result in prolonged procedure time. Therefore, we investigated the efficacy of adding diluted epinephrine to a submucosal injection solution to reduce the procedure time in gastric ESD.

Methods: This international, multicenter, randomized controlled trial was conducted across 12 institutions. Patients with gastric mucosal neoplasia who underwent ESD were eligible. The patients were randomly allocated to either the epinephrine group (1:100,000 diluted epinephrine-added injection solution) or the control group. Randomization was stratified according to lesion location, size, and institution. Patients, endoscopists, and assessors were blinded to the treatment allocation. The primary outcome was the procedure time. Secondary outcomes included the number of intraprocedural hemorrhages requiring the use of hemostatic forceps and postprocedural adverse events.

Results: A total of 800 patients were enrolled, 774 of whom were included in the final modified intention-to-treat analysis. A total of 386 and 388 patients were randomized into the epinephrine and control groups, respectively. The mean (SD) procedure time was significantly shorter in the epinephrine group than in the control group: 60 (46) versus 68 (45) minutes, respectively ($P = .018$). The number of intraprocedural hemorrhages requiring hemostatic forceps was significantly lower in the epinephrine group (mean count: 1.8 vs 3.0; $P < .001$). There were no significant differences in postprocedural adverse events between the groups.

Conclusions: The addition of diluted epinephrine to the injection solution significantly reduces the procedure time for gastric ESD. ([ClinicalTrials.gov: NCT04032119](https://clinicaltrials.gov/ct2/show/study/NCT04032119).) (Gastrointest Endosc 2026;104:387-95.)

INTRODUCTION

Endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) provides high rates of en bloc and R0 resection.^{1,2} Large-scale prospective studies have confirmed excellent overall survival in patients with EGC who met the treatment criteria and underwent gastric ESD, with outcomes comparable to those of surgical resection.^{3,4} ESD is currently considered the standard treatment for eligible cases of EGC.^{5,6}

Gastric ESD involves injecting a solution into the submucosa to expand the submucosal space, which facilitates the dissection of the submucosa along the surface of the muscularis propria without causing perforation. However, because of the abundant vascular networks in the submucosa, including multiple penetrating arteries traversing the muscularis propria, intraprocedural hemorrhage is one of the most common adverse events during gastric ESD. Bleeding during the procedure obscures the endoscopic view, making it difficult to identify the correct dissection plane. The need for hemostasis and repeated reestablishment of the dissection plane prolongs the procedure and may increase the risk of perforation if dissection is performed with a suboptimal view. To mitigate these risks and facilitate gastric ESD, diluted epinephrine is often added to the submucosal lifting solution, at the endoscopist's discretion, to induce vasoconstriction. Although the usefulness of epinephrine has been demonstrated during the endoscopic removal of large pedunculated colonic polyps, its benefit in gastric ESD has not been fully investigated.⁷

A previous single-center retrospective study by our group suggested that adding diluted epinephrine to the injection solution reduced the procedure time during gastric ESD.⁸

Therefore, we conducted a randomized controlled trial to confirm the benefit of adding epinephrine to the submucosal injection solution during gastric ESD.

PATIENTS AND METHODS

Trial design

This was an international, parallel-group, double-blind, randomized controlled trial conducted at 12 institutions—including referral cancer centers, academic hospitals, and general hospitals—across the Asia-Pacific region (Japan, Hong Kong, Korea, and Singapore).

Ethics statement

The trial was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (CUHK–NTEC CREC; Ref. No. 2019.449) on December 12, 2019, in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol was approved by the local ethics committees of all collaborating sites. Minor revisions to the study protocol, including changes to coinvestigators and study duration, were made during the study period. The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04032119) (<https://clinicaltrials.gov/study/NCT04032119>).

NCT04032119) on July 25, 2019. Written informed consent was obtained from all patients before their participation.

Participants

Adult patients (aged ≥ 20 years) with biopsy-proven gastric mucosal low- or high-grade neoplasia⁹ who were scheduled to undergo ESD were assessed for eligibility. Detailed eligibility criteria are provided in [Supplementary Table 1](#) (available online at www.giejournal.org).

Exclusion criteria comprised (1) patients with recurrent or remnant lesions after previous endoscopic resection; (2) lesions arising from a surgical anastomotic site; (3) multiple gastric lesions requiring ESD; (4) marked electrolyte abnormalities; (5) hemostatic or coagulative disorders; (6) dual antiplatelets therapy, warfarin, or oral anticoagulants (a single antiplatelet agent was permitted); (7) vital organ failure involving the heart, lungs, liver, or kidneys; (8) allergy to components of the injection solutions; and (9) any condition deemed by the treating physician as unsuitable for safe ESD.

Randomization and masking

A web-based randomization program (REDCap) assigned patients to undergo gastric ESD with or without the addition of diluted epinephrine to the submucosal injection solution in a 1:1 ratio, using a computer-generated sequence with stratification by institution, lesion size (≤ 2 or > 2 cm), and location (upper/mid or lower stomach). Randomization was performed immediately before the ESD procedure by study personnel who were blinded to the clinical information. The assigned group was communicated with a nurse who was not involved in ESD. The submucosal injection solution containing either diluted epinephrine or no epinephrine was prepared and delivered to the endoscopy room. Patients, endoscopists, and outcome assessors were blinded to the treatment allocation.

Intervention

The operator performing the ESD procedure was either an expert endoscopist (experience > 50 ESD cases) or a nonexpert endoscopist (≤ 50 ESD cases) supervised by an expert. The procedure was conducted according to current standard practice, including lesion marking, submucosal injection outside the markings, mucosal incision, further submucosal injection beneath the lesion, and submucosal dissection for complete lesion removal.¹⁰ When vessels were identified in the submucosal layer, prophylactic coagulation was performed using either an endoscopic knife or hemostatic forceps. Generally, oozing hemorrhages were managed with electrical cauterization via endoknives, whereas spurting hemorrhages were controlled by hemostatic forceps coagulation. Upon completion of the procedure, all patients underwent prophylactic coagulation of the visible vessels at the wound base using coagulation forceps. Post-ESD defects were not closed. A proton pump inhibitor

was administered orally for 8 weeks after the procedure to promote ulcer healing.

Patients randomized to the epinephrine group underwent the procedure with the addition of epinephrine to the injection solution at a standardized final concentration of 1:100,000, whereas those in the control group received the injection solution without epinephrine. The same solution was used throughout the procedure, including the initial lifting for mucosal incision and additional lifting during submucosal dissection. To ensure generalizability, in addition to the inclusion of epinephrine in the submucosal injection solution, all other procedural elements were evaluated according to the standard practices of each participating institution. These included the components of the injection solution, choice of endoscopic knives and accessories, and use of traction techniques. In particular, other components of the injection solution, such as glycerin or hyaluronic acid, were allowed according to the institutional setting to ensure the generalizability of the results to a wide range of clinical practices. A monthly monitoring report was issued to track study progress and adverse event incidence. Study group meetings were held every 6 months to ensure compliance with the study protocol.

Outcomes

The primary outcome was ESD procedure time, defined as the duration from the initiation of the mucosal incision to complete detachment of the resected specimen. The time required for prophylactic coagulation of the visible vessels in the ESD defect after resection was excluded.

Secondary outcomes included intraprocedural hemorrhagic events, defined as significant bleeding requiring the use of coagulation forceps during the procedure. Additional secondary outcomes included maximum intraprocedural blood pressure and pulse, as well as the incidence of grade 2 or higher postprocedural adverse events according to the Common Terminology Criteria for Adverse Events (version 5.0; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf), recorded up to 30 days after the procedure.

Statistical analysis and sample size estimation

Sample size estimation was based on our previous retrospective study, which assumed a mean (SD) ESD procedure time of 80 (50) minutes in the epinephrine group and 90 (60) minutes in the control group.⁸ It was calculated that 788 patients would be required to detect a significant difference with a power of 0.8 and a 2-sided α error level of 0.05. After accounting for potential dropouts, the final target sample size was 800 patients.

Primary analysis was conducted using the intention-to-treat (ITT) principle. A secondary post hoc analysis was conducted using the per-protocol method. The primary outcomes were compared using multiple regression analysis

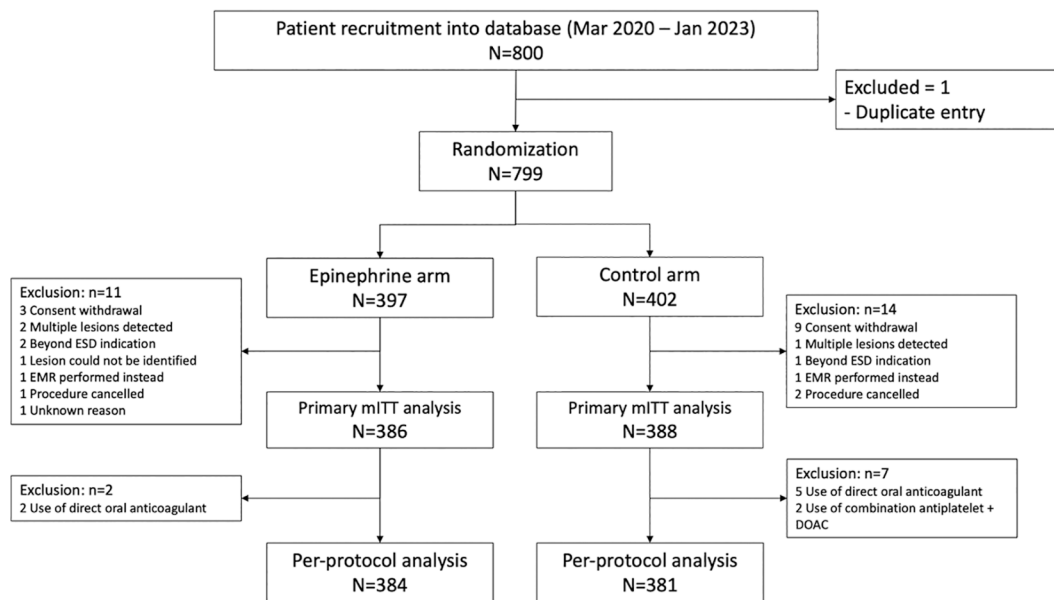


Figure 1. Participant flow diagram. DOAC, Direct oral anticoagulant; ESD, endoscopic submucosal dissection; mITT, modified intention-to-treat.

adjusted for prestratified variables. Secondary outcomes were analyzed using Poisson regression, logistic regression, or multiple regression, depending on the type of variable. An interim analysis was not performed. Posthoc subgroup analyses were performed to evaluate the effect of diluted epinephrine during gastric ESD on lesion location, size, presence of ulcers, institution, endoscopist experience, type of knife, traction technique, and antiplatelet agent use.

The main data analysis was conducted by Toshio Shimokawa using statistical software (IBM SPSS Statistics version 28.0; IBM Corp, Armonk, NY, USA). Statistical significance was set at $P < .05$.

RESULTS

From June 2020 to January 2023, 799 patients were recruited and randomized. Of these, 386 and 388 patients in the epinephrine and control groups, respectively, underwent ESD with the allocated submucosal injection solution and were included in the primary modified ITT analysis. Twenty-five patients were excluded from the primary analysis because of consent withdrawal ($n = 12$), multiple lesions ($n = 3$), ESD not performed because it exceeded the indication criteria ($n = 3$), EMR performed instead ($n = 2$), or other reasons ($n = 3$). The modified CONSORT flowchart is presented in Figure 1.

The baseline demographic and lesion characteristics of the recruited patients are presented in Table 1. The median age of the patients was 72 years (range, 31-94 years), with a predominance of male patients (73%). Sixty-seven (17%) and 58 (15%) patients in the epinephrine and control groups,

respectively, were receiving antiplatelet agents. A total of 365 lesions (46%) were located in the lower stomach, whereas the remaining lesions were located in the upper or middle stomach. Most of the lesions (87%) were ≤ 2 cm in size. More than half of the procedures were performed by expert endoscopists. An insulated-tip knife (IT Knife 2, KD-611L, Olympus Corp, Tokyo, Japan) was the predominant choice of endoscopic knives, followed by needle-type knives (Flush-Knife BT-S, DK2620JI, Fujifilm Corp, Tokyo, Japan; DualKnife J, KD-655, Olympus) and scissor-type knives (ClutchCutter, DP2618DT, Fujifilm). Traction techniques were used in approximately one-fourth of the procedures. A detailed description of the composition of the injection solution and the preferred knife used at each institution is provided in Supplementary Table 1. The mean (SD) histologic specimen sizes were 35 (14) and 34 (12) mm in the epinephrine and control groups, respectively. Adenocarcinomas were found in 342 (89%) and 334 (86%) specimens in the epinephrine and control groups, respectively. The procedural details and pathologic data are summarized in Table 2.

Primary outcome

The mean (SD) procedure times were 60 (46) and 68 (45) minutes in the epinephrine and control groups, respectively, with a crude mean difference (95% CI) of -8.1 (-15 to -1.6) minutes ($P = .014$). After multivariate regression analysis, the addition of diluted epinephrine to the submucosal injection solution significantly reduced the procedure time, with an adjusted mean difference (95% CI) of -7.0 (-13 to -1.2) minutes ($P = .018$) (Table 3).

TABLE 1. Patient and lesion characteristics

	Treatment (N = 386)	Control (N = 388)
Age, median (range)	72 (31-94)	73 (37-90)
Sex		
Male	270 (70%)	294 (76%)
Female	114 (30%)	93 (24%)
Use of antiplatelet agents		
Aspirin	36 (9.4%)	34 (8.8%)
Clopidogrel	14 (3.6%)	7 (1.8%)
None	317 (83%)	328 (85%)
Other	17 (4.4%)	17 (4.4%)
Comorbidities		
DM	67 (17%)	63 (16%)
HT	152 (39%)	159 (41%)
Coronary artery disease	31 (8.0%)	28 (7.2%)
Cerebrovascular disease	20 (5.2%)	23 (5.9%)
Others	36 (9.3%)	28 (7.2%)
Heart rate before ESD (mm Hg), median (range)	71 (41-108)	72 (43.0-120)
Systolic blood pressure before ESD (mm Hg), median (range)	136 (86-192)	134 (63-205)
Tumor longitudinal location		
Upper	60 (16%)	73 (19%)
Middle	133 (32%)	155 (40%)
Lower	195 (51%)	160 (41%)
Tumor circumferential location		
Anterior wall	54 (14%)	65 (17%)
Posterior wall	75 (19%)	68 (18%)
Lesser curvature	167 (43%)	182 (47%)
Greater curvature	90 (23%)	73 (19%)
Endoscopic lesion size		
>2 cm	56 (15%)	42 (11%)
≤2 cm	330 (86%)	346 (89%)
Institution		
CGH (Singapore)	1	2
FUCH (Japan)	55	49
IPCH (Japan)	22	25
Kochi RCH (Japan)	9	13
Kyoto RCH (Japan)	5	3
KUGH (South Korea)	18	18
MGH (Japan)	22	24
NCH (Japan)	2	4
OICI (Japan)	192	196
PWH (Hong Kong SAR)	16	14
SKH (Japan)	3	4
WRCH (Japan)	41	36

CGH, Changi General Hospital; DM, diabetes mellitus; FUCH, Fukuoka University Chikushi Hospital; HT, hypertension; IPCH, Ishikawa Prefectural Central Hospital; Kochi RCH, Kochi Red Cross Hospital; KUGH, Kosin University Gospel Hospital; Kyoto RCH, Kyoto 2nd Red Cross Hospital; MGH, Machida Gastrointestinal Hospital; NCH, Nara City Hospital; OICI, Osaka International Cancer Institute; PWH, Prince of Wales Hospital; SKH, Sapporo Kinentou Hospital; WRCH, Wakayama Red Cross Hospital.

TABLE 2. ESD procedure and pathologic data

	Treatment (N = 386)	Control (N = 388)
Endoscopists		
Nonexpert (≤ 50 cases)	143 (37%)	146 (38%)
Expert (>50 cases)	243 (63%)	242 (62%)
Knife		
Insulated-tip knife	307 (80%)	298 (77%)
Needle-type knife	77 (20%)	86 (22%)
Scissors-type knife	1 (0.3%)	1 (0.3%)
Others	1 (0.3%)	3 (0.8%)
Use of the traction technique	115 (30%)	100 (26%)
Final histology		
Adenocarcinoma	342 (89%)	334 (86%)
High-grade dysplasia	11 (2.8%)	12 (3.1%)
Low-grade dysplasia	23 (6.0%)	33 (8.5%)
Others	10 (2.6%)	9 (2.3%)
Mean histologic lesion size (mm, SD)	15 (13)	13 (11)
Mean histologic specimen size (mm, SD)	35 (14)	34 (12)
Histologic finding of ulcer	30 (7.8%)	18 (4.7%)
Positive HM	3 (0.8%)	6 (1.6%)
Positive VM	8 (2.1%)	11 (2.9%)
R0 resection	370 (97%)	368 (97%)

HM, Horizontal margin; VM, vertical margin.

TABLE 3. Outcome analysis

	Epinephrine group	Control group	Adjusted analysis	P value
Procedure time, min, mean (SD)	60 (46)	68 (45)	MD (95% CI): −7.0 (−13 to −1.2)*	.018
No. of bleeding events requiring the use of hemostatic forceps, count, mean	1.8	3.0	RR (95% CI): 0.59 (0.54-0.65)†	<.001
Adverse events				
Delayed hemorrhage, n (%)	21 (5.5%)	11 (2.8%)	OR (95% CI): 0.53 (0.25-1.1)‡	.096
Intraprocedure perforation, n (%)	10 (2.6%)	6 (1.5%)	OR (95% CI): 0.54 (0.19-1.5)‡	.245
Cardiovascular event, n (%)	1 (0.3%)	0 (0%)	N/A	N/A
Cerebrovascular event, n (%)	0 (0%)	0 (0%)	N/A	N/A
Other adverse events, n (%)	3 (0.8%)	1 (0.3%)	OR (95% CI): 0.33 (0.03-3.3)‡	.346
Maximum systolic blood pressure, mm Hg (controlling for baseline)	148 (26)	145 (25)	MD (95% CI): 3.6 (0.1-7.1)	.042
Maximum heart rate, beats per min (controlling for baseline)	82 (19)	82 (20)	MD (95% CI): 0.03 (−2.6 to 2.7)	.979

MD, Mean difference; N/A, not applicable; OR, odds ratio; RR, risk ratio.

*Multiple regression analysis with stratification factors (including institutional stratum, tumor location, and lesion size) as covariates.

†Poisson regression was used (adjusted for stratification factors as covariates).

‡Logistic/multiple regression analysis with stratification factors (including institutional stratum, tumor location, and lesion size).

Secondary outcomes

The number of intraprocedural bleeding events requiring the use of hemostatic forceps was significantly lower in the epinephrine group (mean: 1.8 vs 3.0), with an adjusted rate ratio (95% CI of 0.59 [0.54-0.65]; $P < .001$). No significant differ-

ences were observed in other postprocedural adverse events, including delayed hemorrhage, intraprocedural perforation, or cerebrovascular or cardiovascular events. A statistically significant increase in the maximum systolic blood pressure was observed in the epinephrine group, with an

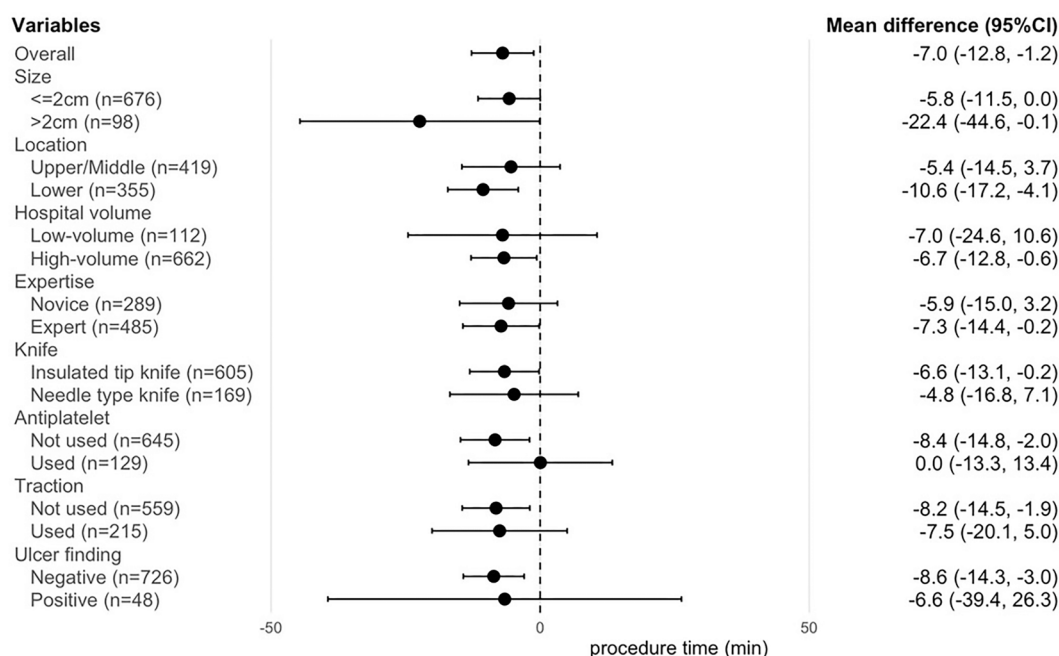


Figure 2. Forrest plot on the subgroup analyses of the primary outcome.

adjusted mean difference of 3.6 mm Hg. No differences were found in maximum heart rate during the procedure (Table 3). There were no cases of delayed perforation in either group, and no patients required salvage surgery for adverse events. One patient died within 30 days of the ESD procedure due to suicide.

For the sensitivity analysis, per-protocol analyses were performed after excluding patients taking oral anticoagulants or multiple antiplatelet agents. The procedure times were 60 and 68 minutes for the epinephrine and control groups, respectively (mean difference: -6.9 minutes; $P = .02$), and the number of intraprocedural bleeding events was 1.8 and 3.0 (risk ratio, 0.59; $P < .001$), which was nearly identical to the findings from the modified ITT analysis.

Posthoc subgroup analyses demonstrated that the benefit of diluted epinephrine was consistent across all subgroups (Fig. 2). The shortening of the procedure time was more obvious in larger lesions as well as in lesions in the lower part of the stomach. In particular, there was a similar trend of improvement for both high- and low-volume centers and among expert and novice endoscopists.

DISCUSSION

In the current study, we demonstrated that adding 1:100,000 epinephrine to the submucosal injection solution shortened the overall procedure time by approximately 10%. To our knowledge, this is the first and largest international randomized trial to date investigating

ESD techniques for EGC. Compared with a large multicenter cohort study published in Japan, the patient and lesion characteristics in our trial were highly comparable.¹¹ Approximately 40% of the lesions were located on the lesser curvature of the stomach, and approximately 80% were located in the middle or lower third. In our study, the R0 resection rate exceeded 97%, which is comparable to the previously reported findings. The incidence of major adverse events, including delayed hemorrhage and intraprocedural and delayed perforations, was similar to that reported in the literature, suggesting that our study reflects general endoscopic practice.

A previous randomized study evaluating clip line-assisted traction during gastric ESD failed to demonstrate an overall reduction in procedure time.¹² The traction technique was only effective in a subset of patients with tumors located in the greater curvature, where gravity did not facilitate dissection. In contrast, epinephrine is readily available and requires only a simple dilution step for addition to the submucosal injection solution during ESD. We believe that the vasoconstrictive effect of epinephrine contributed to a smoother procedure. Reduced bleeding during both mucosal incision and submucosal dissection may facilitate accurate identification of the incision and dissection planes because less time is needed for cleansing and suctioning when the visual field is not obscured by blood. This was supported by one of our study outcomes, which showed fewer instances of intraprocedural hemorrhage requiring hemostatic forceps cauterization. Importantly, the addition of diluted epinephrine shortened the procedure time to a larger effect among lesions >2 cm in size (-22.39 vs -5.77 minutes).

However, this difference was not statistically significant because of the small sample size. This suggests that in difficult procedures involving large lesions, the effect of epinephrine could be more pronounced. Although there was a statistically significant numerical increase in the maximum systolic blood pressure of 3.6 mm Hg, we did not consider this finding clinically relevant. After adjusting for baseline values, the increase in blood pressure was similar between the epinephrine and control groups (26 and 25 mm Hg, respectively). No differences in cardiovascular or cerebrovascular adverse events were observed between the 2 groups. Moreover, we did not observe an increase in excessive postprocedural pain after ESD with an epinephrine-containing injection solution. This finding differs from that of a previous small randomized study that reported significant pain associated with epinephrine use during colonic EMR.

Recently, new image enhancement modes using a special spectrum of light, such as Red Dichromatic Imaging (RDI; Olympus Medical Corporation) and Amber Color Imaging (ACI; Fujifilm Corp), have been developed. These modalities highlight the bleeding point, thereby potentially reducing the time for hemostasis and procedure time.^{13,14} However, a recent randomized controlled trial did not demonstrate the benefit of RDI in reducing the time required for hemostasis and the ESD procedure.¹⁵ Because these modes were not available during the study period, we could not evaluate the effect of diluted epinephrine under RDI or ACI modes.

Although not statistically significant, a higher incidence of delayed hemorrhage was observed in the epinephrine group. Although prophylactic coagulation of visible vessels over the postresection wound is routinely performed, this could be overlooked because of the vasoconstrictive effect of epinephrine. It remains imperative that careful examination and coagulation of visible vessels should be performed during all gastric ESD procedures. The latest technologies, such as RDI/ACI,^{13,14} or artificial intelligence–assisted coagulation, may further improve the accuracy of prophylactic coagulation.¹⁶ Moreover, emerging evidence also suggests that complete closure of the ESD wound in high-risk patients may reduce the risk of delayed hemorrhage, which could also potentially further mitigate the risks involved in patients with large defects, renal impairment, and those receiving high-risk medications.¹⁷

Our study has several strengths. This international randomized trial was conducted across 12 institutions in 4 Asian countries. The participating centers varied in annual ESD case volumes, ranging from low to high, according to a recent large-scale Korean nationwide database study.¹⁸ We included both novice and expert endoscopists and allowed procedural variation in the choice of endoscopic knife and use of counter-traction techniques. The large sample size helped minimize selection bias, thereby enhancing the

generalizability of our findings to patients undergoing gastric ESD in routine clinical settings.¹⁹ The benefit of adding diluted epinephrine was consistently observed in almost all subgroups, especially among high- and low-volume centers and expert and novice endoscopists, indicating that adding epinephrine may be an acceptable universal strategy during gastric ESD.

The current study has several limitations. First, aside from procedure time and intraprocedural bleeding events, we did not demonstrate differences in other clinically important outcomes, such as R0 resection rates or postprocedural adverse events. Given the low incidence of adverse events after gastric ESD, a prospective study powered to detect such differences requires an impractically large sample size. Second, we did not quantify the volume of intraprocedural bleeding because accurate estimation was not feasible because of extensive water flushing and the tendency for a substantial volume of blood to drain into the duodenum without being suctioned during gastric ESD. Instead, the number of bleeding events requiring coagulation forceps was used as a surrogate measure. Third, we did not record the total volume of injection solution used during each procedure. This was based on the assumption that the volume depended primarily on the lesion size rather than on the addition of diluted epinephrine. Furthermore, intraprocedural injection via a water-jet knife or scope-based water flushing may dilute the epinephrine concentration. However, we assumed that any changes in the epinephrine concentration because of these additional injections had a minimal effect on the study outcomes. Fourth, we were unable to calculate the dissection speed, which is commonly quoted as an outcome measure in various ESD studies, because of the lack of the short-axis size of the specimens. However, we believe that the potential bias arising from the different lesion sizes between the 2 groups was minimized because of the large sample size and stratification by lesion size before randomization. Subgroup analysis also showed that the benefit of epinephrine was consistent regardless of lesion size. Finally, although the operator was blinded to the addition of epinephrine to the injection solution, mucosal blanching was sometimes observed after injection of the epinephrine-added solution, revealing the type of solution used during ESD, which could potentially lead to bias in the endoscopists. Another consideration is that the proportion of patients taking antiplatelet agents, particularly nonaspirin antiplatelet agents, was low, and patients receiving anticoagulants were excluded. Therefore, it was difficult to assess the effects of epinephrine in this group of patients.

In conclusion, the addition of diluted epinephrine to a submucosal injection solution during gastric ESD shortened the procedure time and reduced intraprocedural bleeding. This technique can be recommended as a routine practice for patients undergoing gastric ESD.

DATA TRANSPARENCY STATEMENT

Complementary anonymized data, analysis methods, and research materials will be made available to other researchers at the time of publication for 5 years, according to specific requests.

DISCLOSURE

The following authors disclosed financial relationships: N. Uedo: Lecture fees from Olympus Medical Systems Co, Ltd, FUJIFILM Co, Ltd, Boston Scientific Japan, Daiichi-Sankyo Co, Ltd, Takeda Pharmaceutical Co, Ltd, EA Pharma Co, Ltd, Otsuka Pharmaceutical Co, Ltd, AstraZeneca Co, Ltd, Miyarisan Pharmaceutical Co, Ltd, AI Medical Service Co, Ltd, 3-D Matrix Ltd, and FUJIFILM Medical Co, Ltd. H. C. Yip: Lecture fees from Olympus Medical Systems Co, Ltd, Cornerstone Robotics Ltd, Medtronic Hong Kong Medical Ltd, and Creo Medical Co, Ltd; research collaboration: Olympus Medical Corporations Ltd. P. W. Y. Chiu: Research collaboration: Olympus Co, Ltd and Boston Scientific; advisor: EndoVision and EndoMaster. T. Kawamura: Speaker for Olympus Marketing Corporation. All other authors disclosed no financial relationships. This study was supported by funds from the Asian Endoscopy Research Forum for the application of clinical trial insurance in Hong Kong.

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Abbreviations: ACI, Amber Color Imaging; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; ITT, intention-to-treat; RDI, Red Dichromatic Imaging.



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SUPPLEMENTARY TABLE 1. Standard settings for gastric ESD at each institution

Hospital	Standard setting
CGH (Singapore)	Solution: hypromellose solution Dye: none Preferred knife: needle-type knife
FUCH (Japan)	Solution: sodium alginate Dye: indigo carmine Preferred knife: insulated-tip knife (85%), needle-type knife (13%), and scissor-type knife (2%)
IPCH (Japan)	Solution: sodium alginate Dye: indigo carmine Preferred knife: insulated-tip knife
Kochi RCH (Japan)	Solution: sodium hyaluronate Dye: indigo carmine Preferred knife: needle-type knife
Kyoto RCH (Japan)	Solution: sodium hyaluronate Dye: indigo carmine Preferred knife: needle-type knife
KUGH (South Korea)	Solution: normal saline solution Dye: indigo carmine Preferred knife: insulated-tip knife
MGH (Japan)	Solution: sodium hyaluronate Dye: indigo carmine Preferred knife: insulated-tip knife
NCH (Japan)	Solution: glycerin Dye: none Preferred knife: needle-type knife
OICI (Japan)	Solution: sodium hyaluronate Dye: none Preferred knife: insulated-tip knife (91%) and needle-type knife (9%)
PWH (Hong Kong SAR)	Solution: normal saline solution + hyaluronic acid Dye: none Preferred knife: needle-type knife (54%) and insulated-tip knife (46%)
SKH (Japan)	Solution: sodium hyaluronate Dye: indigo carmine Preferred knife: insulated-tip knife
WRCH (Japan)	Solution: sodium hyaluronate Dye: indigo carmine Preferred knife: needle-type knife (85%) and insulated-tip knife (15%)

CGH, Changi General Hospital; FUCH, Fukuoka University Chikushi Hospital; IPCH, Ishikawa Prefectural Central Hospital; Kochi RCH, Kochi Red Cross Hospital; KUGH, Kosin University Gospel Hospital; Kyoto RCH, Kyoto 2nd Red Cross Hospital; MGH, Machida Gastrointestinal Hospital; NCH, Nara City Hospital; OICI, Osaka International Cancer Institute; PWH, Prince of Wales Hospital; SKH, Sapporo Kinentou Hospital; WRCH, Wakayama Red Cross Hospital.