

Efficacy of submucosal bupivacaine injection for pain relief after endoscopic submucosal dissection

A multicenter, prospective, randomized controlled, and double-blind trial

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Abstract

Background and aim: Although abdominal pain is a common adverse event related to endoscopic submucosal dissection (ESD), it can be sometimes underestimated by endoscopists. There are some endoscopic interventions available for the prevention of post-ESD pain, but their efficacy has not been established. We investigated whether a submucosal injection of bupivacaine (BP) can reduce procedure-related abdominal pain compared with the standard method.

Methods: We performed a multicenter, double-blinded, randomized controlled trial of 86 adult patients referred for ESD as treatment for gastric neoplasms. Patients were randomly assigned to either the BP submucosal or conventional solution group. Questionnaires were collected when the study began (baseline) and immediately after ESD, as well as at 6, 12, and 24 hours post-operatively. The primary outcome was indicated by the visual analog scale (VAS) evaluated at 6 hours after procedure.

Results: There were no significant differences in primary outcomes between groups and among all time points (immediately, 12, and 24 hours after ESD). The VAS and short-form McGill pain (SF-MP) scores were higher immediately after ESD than at 6, 12, or 24 hours post-operatively. The incidence of abdominal pain immediately after ESD was 94.0% (78/83) for all patients of both groups, and there was no significant difference between the 2 groups in the rate of abdominal pain immediately after ESD (BP group 37/40 [92.5%] versus non-BP group 41/43 [95.3%], $P = .934$). In univariable and multivariable analyses, BP did not have protective effect on post-ESD abdominal pain.

Conclusions: Submucosal BP injection does not promote pain relief or mitigate the effects of post-ESD abdominal pain.

Abbreviations: BP = bupivacaine, Ce = concentration, ESD = endoscopic submucosal dissection, NSAID = non-steroidal anti-inflammatory drug, OR = odds ratio, PPI = proton pump inhibitors, SF-MP = short-form McGill pain, VAS = visual analog scale.

Keywords: abdominal pain, bupivacaine, endoscopic submucosal dissection, local anesthesia, submucosal injection

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1. Introduction

Endoscopic submucosal dissection (ESD) is becoming the standard procedure to treat gastric neoplasm because an en bloc resection by ESD provides exact histological information such as depth of invasion, lateral margin involvement, and even complete and/or curative resectability.^[1,2] However, although ESD is a minimally invasive procedure for gastric neoplasm compared with surgical resection, abdominal pain after ESD is very common and delays discharge after intervention.^[3] Additionally, endoscopists tend to underestimate or ignore post-ESD pain.^[3] According to our experience, moderate to severe pain develops in some patients, especially 6 to 24 hours after ESD. Ambiguous abdominal pain after ESD might be attributed to mucosal defects, transmural air leaks, and electrical burns or thermal injury extending to the remnant layer.^[4-6] Nevertheless, except small number of trials,^[7-9] no management strategies for post-ESD abdominal pain have been reported yet.

Among the relevant reports, Kim et al^[3] demonstrated that bupivacaine (BP) injection to the ulcer bed after full dissection of the submucosal layer as a topical analgesic agent was more effective for pain reduction especially 6 hours after procedure,

and triamcinolone in combination with BP had a synergic effect, prolonging analgesia. Generally, BP is used for management of chronic pain derived from visceral organs or acute pain from surgical intervention.^[10] Although the mechanisms are not entirely clear, the aforementioned results suggest that submucosal BP injection may have preventive use similar to local analgesic agents that are administered before painful stimuli (burn injuries due to electrical current from surgical knife during ESD) to desensitize the central and peripheral nervous systems and promote relief from post-procedural pain. However, Kim's method may have some limitations: First, the injection solution in the post-ESD ulcer base might influence the occurrence of inflammation of the peritoneal cavity because an injection needle can deeply and transmurally penetrate the gastric wall, resulting in temporary irritation of the peritoneum. Second, the injection needle used for delivery of the solution could lead to additional mucosal injury and even bleeding. Therefore, we believe that a submucosal BP injection can be more effective and safer than a direct injection to the ulcer bed as it reduces the risk of procedure-related additional injury.

Until now, it has been unclear whether the theoretical benefit of a submucosal BP injection actually results in superior outcomes compared with the standard method. Furthermore, no study has evaluated the efficacy of this method. We aimed to conduct a randomized controlled study to compare the administration of topical BP using a submucosal injection with the standard method for reduction of post-ESD abdominal pain.

2. Methods

2.1. Study population and randomization

Between 1 October 2014 and 14 June 2016, we prospectively evaluated consecutive patients aged 20 years or older who were scheduled to undergo ESD for pathologically diagnosed or clinically suspected gastric adenoma or cancer at the Hallym Medical Center. The exclusion criteria were as follows:

- (1) declining to provide informed consent;
- (2) American Society of Anesthesiology risk Class 3 or higher;
- (3) severe hepatic disease or cardiopulmonary or renal dysfunction;
- (4) current use of analgesics including non-steroidal anti-inflammatory drugs (NSAIDs) during the preceding week;
- (5) allergy to BP or other amide-type local anesthesia;
- (6) confirmation of any other disease that could induce abdominal pain similar to post-ESD pain;
- (7) presence of multiple lesions requiring endoscopic resection;
- (8) currently pregnant or breast feeding; and
- (9) unable to assess pain due to severe psychiatric or neurological disease.

The classic (standard) indication used for determining a patient's eligibility for the procedure.^[11] All patients were randomly assigned to the BP solution (BP group) group or the conventional solution group (non-BP group). Randomization was performed using a table (block randomization method according to number of patients assigned to each center) of computer-generated random numbers prepared by a research nurse who was not involved in the ESD procedure. The allocation sequence was concealed using opaque sealed envelopes, and neither the physicians nor the patients were aware of the treatment allocation. Allocation occurred after sedation of the patient. The solutions were prepared by a third physician who was involved in this study, according to a random table.

2.2. Endoscopic procedures and local injection protocol

All ESD interventions were performed by experienced endoscopists, who had previously performed over 200 ESD procedures according to a standard ESD protocol. Oxygen was supplied via the nasal cannula at a rate of 2 to 5 L per minute according to oxygen saturation, and all vital signs were monitored in real time and recorded every 5 minutes by an assistant nurse. Propofol was administered by the target-controlled infusion (TCI) method regulated by a computer-controlled infusion pump at an infusion rate that was automatically adjusted by software. The procedure was initiated after reaching the initial targeted effect-site concentration (C_e) of 4 $\mu\text{g}/\text{mL}$, using the Schnider pharmacokinetic model (maximal flow rate <700 mL/h).^[12] The initial C_e was determined according to previously reported results.^[13] In order to prevent oversedation, the C_e was adjusted according to each endoscopist's preference in increments of 0.5 $\mu\text{g}/\text{mL}$ by registered nurses who were certified in advanced cardiac life support and had completed a structured training program conducted regularly in our hospital for propofol administration under the supervision of endoscopists.^[14,15] The target level of sedation was such that patients were not expected to respond verbally, but they were responsive to painful stimuli from the ESD.

Additionally, any drugs including analgesics such as opioids except sedative agents and hyoscine butylbromide used during the procedure were not permitted to accurately evaluate pain. In all ESD procedures, CO_2 was routinely supplied using a CO_2 regulation unit (OLYMPUS UCR; Olympus Medical Systems) connected to a CO_2 tank. The ESD procedure was conducted by following the standard protocol: circumferential marking, marginal pre-cutting (incision), and submucosal dissection and/or hemostasis. After the target lesion was identified using indigo carmine staining, marking dots were circumferentially made along an imaginary line 5 mm outside of the lateral margin of the lesion, using either a flex knife (Flex Knife; KD-630L, Olympus Optical, Tokyo, Japan) or dual knife (Olympus Optical, Tokyo, Japan), according to the endoscopists' discretion. After marking the normal tissue surrounding the lesion, the first 20 mL of submucosal injection solution (according to the patient's group) was administered evenly to the circumferential outer margin of marking dots. First, the incision of the mucosa was made with a flex knife or dual knife, which was followed by circumferential mucosal cutting at the imaginary outer line 5 mm from the marking dots with a flex knife or dual knife and/or insulated-tip (IT) knife. After completion of pre-cutting, the submucosal dissection was carried out with direct visualization of the submucosal layer. Additional submucosal injections of only the conventional solution (saline with diluted epinephrine and indigo carmine, without BP), were uniformly administered in both groups. The second-look endoscopic findings performed 48 hours after the ESD procedure were classified into 6 categories based on Forrest's classification: Ia, spurting bleeding; Ib, oozing bleeding; IIa, visible vessel; IIb, adherent clot; IIc, black spot; and IIIa, clean base.^[16]

As previously noted, we used 4 mL of 0.5% BP 20 mg/4 mL/A (20 mg; AstraZeneca, Seoul, Korea), 15 mL of normal saline, 0.5 mL of 0.8% indigo carmine dye 40 mg/5 mL/A (4 mg; Korea United Pharm, Seoul, Korea), and 0.5 mL of 0.1% epinephrine 1 mg/mL/A (0.5 mg; Danhan Pharm, Seoul, Korea) for the BP group in this study. On the other hand, we used the conventional solution consisting of 19 mL of normal saline, 0.5 mL of 0.8%

indigo carmine dye, and 0.5 mL of 0.1% epinephrine for the non-BP group. After administration of the first 20 mL of submucosal solution evenly to the circumferential outer margin of the marking dots for each group by using a 23-gauge needle injection catheter (NM-200L-0423; Olympus), only conventional solution was injected into the submucosal layer. Once the needle catheter was inserted into the submucosal layer, the endoscopist confirmed that there was no blood reflex. Next, the assistant nurse would begin injecting the solution and stopped when the lesion was sufficiently lifted.

2.3. Main outcome measurements

Post-ESD abdominal pain was evaluated during the hospital stay. To assess post-ESD abdominal pain, patients completed a questionnaire regarding the degree of abdominal pain experienced using the visual analog scale (VAS)^[17] that ranged from 0 (no pain) to 10 (intolerable), and the short-form McGill pain (SF-MP) score; the assessment was carried out immediately before and after the ESD procedure in both groups by an independent research assistant blinded to the randomization. Subsequently, patients were contacted 6, 12, and 24 hours after ESD to complete a final questionnaire to re-evaluate the presence of abdominal pain. The severity of abdominal pain was categorized as mild (VAS score 1–3), moderate (VAS score 4–6), and severe (VAS score 7–10). Furthermore, the SF-MP score consisted of a 15-adjective checklist (11 sensory and 4 affective dimensions) of pain where each dimension was rated on a 4-point intensity scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Thus, total SF-MP scores ranged from 0 to 45, with a higher score indicating higher intensity pain.^[18,19] The primary end point of this study was VAS evaluated at 6 hours after procedure because pain intensity is maximum at this time point, as previously reported.^[3,8] The secondary outcomes included the SF-MG pain score, need for painkillers after ESD, procedure-related adverse events, second-look endoscopic findings, and the length of hospital stay. Proton pump inhibitors (PPI) were routinely administered in all patients that underwent ESD. If a patient needed additional analgesics, pethidine HCl (pethidine HCl, 25 mg/0.5 mL/A, Jeil, Korea) was given once intramuscularly. Patients who complained of sustained pain after the first pethidine administration were given 1 more injection, regardless of time.

2.4. Statistical analysis

Our main objective was to assess the effectiveness of the submucosal BP injection method compared with the conventional solution. The sample size was based on the prevalence (39%) of post-ESD abdominal pain reported among patients in a previous preliminary case-control pilot study.^[7] In order to achieve power of at least 0.80 to detect a 27% absolute difference between the 2 groups at an alpha level of 0.05, the number of samples required was 40 patients per group. Assuming a 5% dropout rate, the final sample size was set at 43 patients per group.

Continuous and categorical variables were presented as mean with standard deviation and frequency with proportion, respectively. The chi-square test was used to compare categorical variables, and the 2-sample *t* test was used to compare continuous variables. Risk factors for post-ESD abdominal pain were examined by univariate and multivariate analyses, and calculated with an odds ratio (OR) and 95% CI using the logistic regression method. Two-sided *P* values were calculated and 5% was

considered to indicate significance. All statistical analyses were conducted using the statistical software R (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

2.5. Ethics statement

The study protocol was approved by the institutional review board of the ethics committee of the Hallym Medical Center before the initiation of the study (2014–197 in Dongtan Sacred Heart Hospital and 2014-122 in Chuncheon Sacred Heart Hospital), and was conducted in accordance with the latest Declaration of Helsinki for Medical Research Involving Human Subjects. All patients provided written informed consent before enrollment. This trial was registered with the International Clinical Trials Registry Platform, no. (KCT 0002894). All authors had access to the study data, and they reviewed and approved the final manuscript.

3. Results

3.1. Patient characteristics

A total of 101 consecutive patients with the aforementioned characteristics were screened to determine eligibility for this study. Among them, 15 were excluded due to the following reasons: declining to provide informed consent (*n*=4), American Society of Anesthesiology risk Class 3 or higher (*n*=6), severe liver disease, heart disease, or renal dysfunction (*n*=3), or current use of analgesics including NSAIDs during the preceding week (*n*=2). As a result, 86 patients were randomly assigned either to the BP group (*n*=43) or non-BP group (*n*=43). Furthermore, 3 patients in the BP group were excluded from the study because of unexpected multiple lesions. Therefore, 83 patients were included in the final analysis (Fig. 1).

3.2. Baseline patient characteristics

Table 1 shows the baseline characteristics of the 2 groups. The mean ages were 65.9 and 59.6 years in the BP and non-BP groups, respectively, and there was a significant difference (*P* = .018). The proportion of male patients did not differ between the groups (BP vs non-BP: 75.0% vs 69.8%, *P* = .774). Additionally, no differences in body mass index, smoking history, and alcohol intake were found. In both groups, low-grade dysplasia in a previous biopsy report was the most common indication for ESD (BP vs non-BP: 52.5% vs 62.8%). Furthermore, early gastric cancer (EGC) type IIa in endoscopic findings was the most common morphological classification (BP vs non-BP: 35.0% vs 37.2%). In addition, the maximum diameter of the lesion did not differ between groups (BP vs non-BP: 19.8 ± 10.5 vs 17.7 ± 7.7 mm, *P* = .316). Although there was no significant difference, the presence of *Helicobacter pylori* in the non-BP group was higher than in the BP group (BP vs non-BP: 32.5% vs 51.2%, *P* = .189).

3.3. Procedure-related outcomes

Procedure-related outcomes are presented in Table 2. The resection method did not differ between the groups (for ESD with full dissection, BP vs non-BP: 85.0% vs 81.4%, *P* = .885). In terms of devices for precutting and dissection, no significant difference was found between both groups (*P* = .816 and *P* = .080, respectively). In addition, the total procedure time and coagulation time did not differ between groups (BP vs

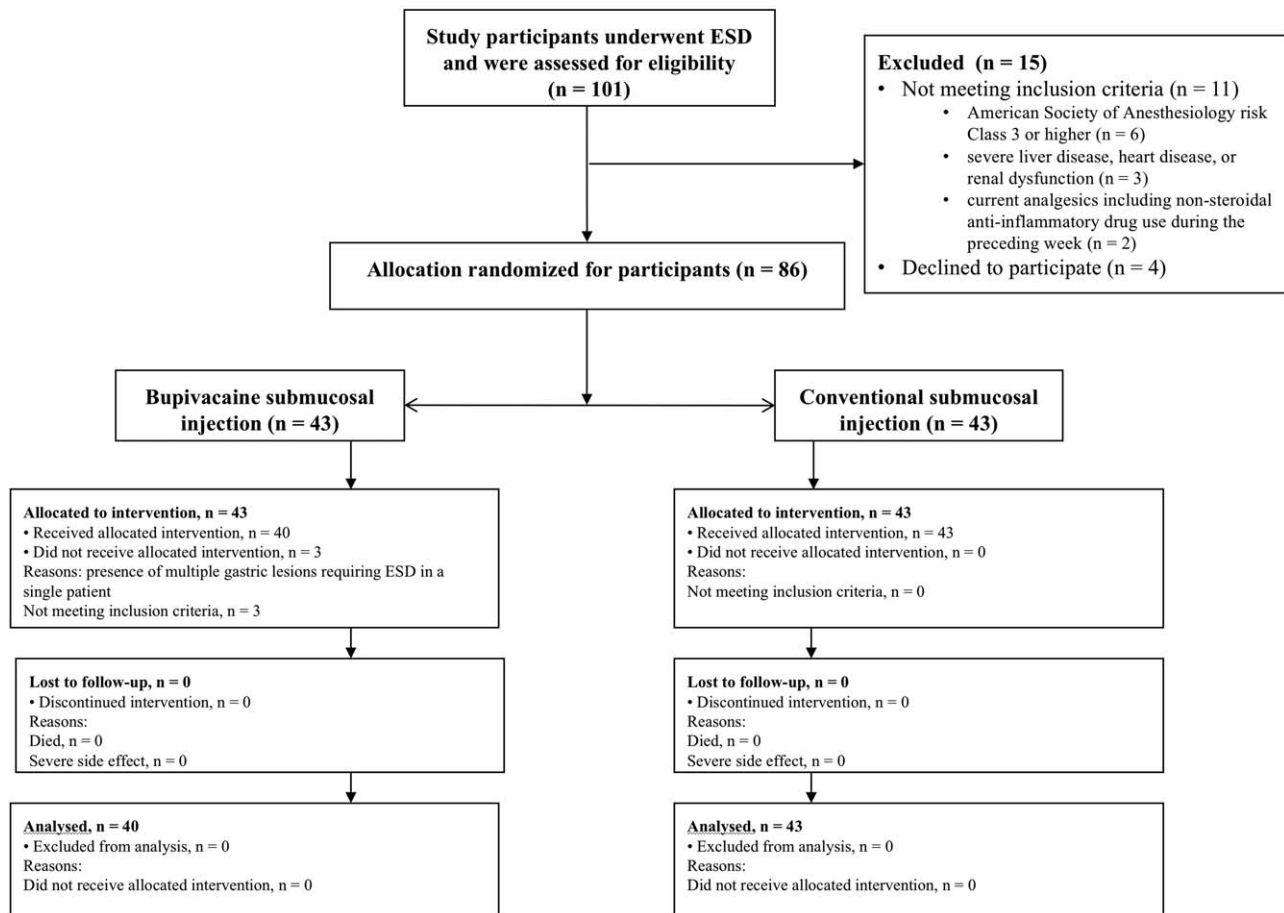


Figure 1. Flow chart of patients in the randomized double-blind trial.

non-BP: 48.5 ± 27.8 vs 42.0 ± 23.5 minutes, $P = .250$ and 9.8 ± 13.7 vs 8.4 ± 8.7 , $P = .575$, respectively). Total administered dosage of propofol was similar between groups (577.0 ± 361.5 vs 627.0 ± 366.5 , $P = .534$). Successful en bloc resection rate was also similar between groups (82.5% vs 86.0% , $P = .887$). In regard to post-ESD bleeding within 48 hours and after 48 hours, there were no differences between the groups. Furthermore, the size of specimen after ESD did not differ between the groups (BP vs. non-BP: 31.6 ± 10.2 vs 29.3 ± 7.7 mm, $P = .259$). Other post-ESD pathological findings such as lateral and vertical margin positivity, lymphovascular invasion positivity, and perineural invasion positivity were also similar in both groups. In particular, there were similar proportions of curative resections in both groups (BP vs non-BP: 31 [77.5%] vs 38 [88.4%], $P = .304$).

3.4. Post-ESD abdominal pain

The incidence of abdominal pain immediately after ESD was 94.0% (78/83) for all patients in both groups (Table 3). The VAS and SF-MP scores were higher immediately after ESD than at 6, 12, or 24 hours post-operatively (Fig. 2). There was no significant difference between the 2 groups in the rate of abdominal pain immediately after ESD (BP group 37/40 [92.5%] vs non-BP group 41/43 [95.3%], $P = .934$) as well as at all time points (6, 12, or 24 hours after ESD). The mean VAS and SF-MP scores immediately

after ESD were lower in the non-BP group than in the BP group (4.7 ± 2.5 vs 5.4 ± 3.1 , $P = .301$ and 5.0 ± 3.1 vs 5.5 ± 3.6 , $P = .541$, respectively), without significant difference. The mean VAS score was graded as mild in 11 patients (27.5%), moderate in 13 patients (32.5%), and severe in 13 patients (32.5%) in the BP group. In the non-BP group, there were 13 (30.2%) patients with mild scores, 19 (44.2%) with moderate scores, and 9 (20.9%) with severe scores, although there was no significant difference between both groups ($P = .549$). Abdominal pain persisted in most patients until the day after the procedure without significant difference between groups (BP group 28/40 [70.0%] vs non-BP group 33/43 [76.7%], $P = .655$). Moreover, there was no statistically significant difference between the groups regarding the length of hospital stay (4.6 ± 2.1 in BP group vs 4.0 ± 0.8 in non-BP group, $P = .127$).

Potential patient- and procedure-related risk factors for post-ESD abdominal pain were analyzed in patients of both groups (Table 4). In univariable analysis, BP did not show analgesic effect on post-ESD abdominal pain (OR [95% CI] of non-BP = 1.90 [0.44–9.83], $P = .4003$). In addition, no variable was identified as a risk factor for post-ESD abdominal pain. Multivariable analysis also showed that BP did not have a protective effect on post-ESD abdominal pain, even after adjusting for potentially confounding variables including age, sex, tumor size, procedure and coagulation time, en bloc

Table 1
Baseline characteristics of enrolled patients.

Characteristics	BP (N = 40)	Non-BP (N = 43)	P
Sex (male, n [%])	30 (75.0%)	30 (69.8%)	.774
Age (mean ±SD, yr)	65.9 ± 10.7	59.6 ± 12.9	.018
BMI (mean ±SD, kg/m ²)	24.8 ± 3.5	25.1 ± 3.8	.735
Smoking	8 (20.0%)	12 (27.9%)	.559
Alcohol	12 (30.0%)	16 (37.2%)	.644
Biopsy before ESD			.052
- AMD	1 (2.5%)	2 (4.7%)	
- APD	2 (5.0%)	0 (0.0%)	
- AWD	2 (5.0%)	0 (0.0%)	
- chronic gastritis	0 (0.0%)	1 (2.3%)	
- HGD	12 (30.0%)	5 (11.6%)	
- LGD	21 (52.5%)	27 (62.8%)	
- Regenerative atypia	2 (5.0%)	8 (18.6%)	
Endoscopic class			.669
- EGC type I	3 (7.5%)	5 (11.6%)	
- EGC type IIa	14 (35.0%)	16 (37.2%)	
- EGC type IIa + b	1 (2.5%)	0 (0.0%)	
- EGC type IIa + c	5 (12.5%)	3 (7.0%)	
- EGC type IIa + III	0 (0.0%)	1 (2.3%)	
- EGC type IIb	13 (32.5%)	10 (23.3%)	
- EGC type IIb + c	1 (2.5%)	3 (7.0%)	
- EGC type IIc	3 (7.5%)	5 (11.6%)	
Size of lesion (maximal diameter, mm)	19.8 ± 10.5	17.7 ± 7.7	.316
Location of lesion 1			.720
- Angle	6 (15.0%)	5 (11.6%)	
- Antrum	20 (50.0%)	23 (53.5%)	
- Cardia	1 (2.5%)	0 (0.0%)	
- High body	3 (7.5%)	1 (2.3%)	
- Lower body	6 (15.0%)	6 (14.0%)	
- Mid body	2 (5.0%)	3 (7.0%)	
- Pylorus	2 (5.0%)	5 (11.6%)	
Location of lesion 2			.136
- AW	5 (12.5%)	9 (20.9%)	
- AW/LC	0 (0.0%)	2 (4.7%)	
- GC	8 (20.0%)	6 (14.0%)	
- LC	20 (50.0%)	13 (30.2%)	
- PW	6 (15.0%)	13 (30.2%)	
- PW/LC	1 (2.5%)	0 (0.0%)	
H. pylori Positive (n [%])			.189
- Negative	13 (32.5%)	12 (27.9%)	
- Positive	13 (32.5%)	22 (51.2%)	
- Unknown	14 (35.0%)	9 (20.9%)	

Categorical variables are presented as n (%) and comparisons were made with chi-squared tests unless otherwise stated. Continuous variables are presented as mean ±SD and a comparison was made with Student t test.

AMD moderately differentiated adenocarcinoma, APD = poorly differentiated adenocarcinoma, AW = anterior wall, AWD = well differentiated adenocarcinoma, BMI = body mass index, BP = bupivacaine, EGC = early gastric cancer, GC = great curvature, HGD = high grade dysplasia, LC = lesser curvature, LGD = low grade dysplasia, PW = posterior wall.

resection, and final pathology (OR [95% CI] of non-BP = 0.35 [0.02–4.30], P = .4131).

4. Discussion

Abdominal pain is the most common adverse event after ESD, and it is occasionally underestimated or overlooked by endoscopists. In order to manage post-ESD abdominal pain, several interventions such as systemic or topical analgesia (BP) and steroid administration have been developed. Nevertheless, up till now, pain management methods for ESD have not been effective.

Table 2
Comparison of procedure-related outcomes between the groups.

Characteristics	BP (N = 40)	Non-BP (N = 43)	P
Resection method (n [%])			.885
- ESD with full dissection	34 (85.0%)	35 (81.4%)	
- ESD with snaring	6 (15.0%)	8 (18.6%)	
Device for precutting (n [%])			.816
- Dual + IT knife	4 (10.0%)	7 (16.3%)	
- Dual knife	18 (45.0%)	20 (46.5%)	
- Flex + IT knife	11 (27.5%)	10 (23.3%)	
- Flex knife	7 (17.5%)	6 (14.0%)	
Device for dissection (n [%])			.080
- Dual + IT knife	4 (10.0%)	1 (2.3%)	
- Dual knife	0 (0.0%)	4 (9.3%)	
- Flex + IT knife	6 (15.0%)	10 (23.3%)	
- IT knife	30 (75.0%)	28 (65.1%)	
Submucosal injection (mL)	53.2 ± 26.8	60.2 ± 44.5	.387
Procedure time (min)	48.5 ± 27.8	42.0 ± 23.5	.250
Coagulation time (min)	9.8 ± 13.7	8.4 ± 8.7	.575
Propofol (mg)	577.0 ± 361.5	627.0 ± 366.5	.534
En bloc resection (n [%])	33 (82.5%)	37 (86.0%)	.887
Post ESD bleeding within 48 hours (n [%])	2 (5.0%)	1 (2.3%)	.949
Post ESD bleeding after 48 hours (n [%])	1 (2.5%)	0 (0.0%)	.971
Final pathology (n [%])			.006
- AMD	12 (30.0%)	5 (11.6%)	
- APD	2 (5.0%)	2 (4.7%)	
- AWD	6 (15.0%)	7 (16.3%)	
- chronic gastritis	0 (0.0%)	1 (2.3%)	
- HGD	11 (27.5%)	2 (4.7%)	
- LGD	8 (20.0%)	22 (51.2%)	
- LGD	0 (0.0%)	2 (4.7%)	
- Regenerative atypia	0 (0.0%)	2 (4.7%)	
- Undiff	1 (2.5%)	0 (0.0%)	
Size of specimen (mm)	31.6 ± 10.2	29.3 ± 7.7	.259
Lateral margin positive (n [%])	6 (15.0%)	2 (4.7%)	.221
Vertical margin positive (n [%])	3 (7.5%)	0 (0.0%)	.215
Lymphovascular invasion positive (n [%])	0 (0.0%)	1 (2.3%)	1.000
Perineural invasion positive (n [%])	2 (5.0%)	0 (0.0%)	.442
Depth of invasion (n [%])			.093
- pT1a	23 (57.5%)	14 (32.6%)	
- pT1b	3 (7.5%)	4 (9.3%)	
- pTis	14 (35.0%)	23 (53.5%)	
- Unkown	0 (0.0%)	2 (4.7%)	
Curative resection (n [%])	31 (77.5%)	38 (88.4%)	.304

AMD moderately differentiated adenocarcinoma, APD = poorly differentiated adenocarcinoma, AWD = well differentiated adenocarcinoma, ESD = endoscopic submucosal dissection, HGD = high grade dysplasia, IT = insulated-tip, LGD = low grade dysplasia.

The results of our study show that the incidence of abdominal pain immediately after ESD was 95.3% (78/83) overall, and submucosal BP injection did not significantly reduce the incidence of post-procedure pain (BP group 37/40, 92.5%). This overall incidence of abdominal pain in patients with or without BP was relatively higher than previously reported incidence rate (53.8%),^[20] even though 1 report^[9] demonstrated that 98% of patients experienced abdominal pain following ESD. The factors responsible for this difference were unclear, but there are many risk factors for abdominal pain after ESD. According to risk factor analysis of post-ESD pain in one recent study,^[20] this pain might be a result of mucosal defect in the post-ESD artificial ulcer, chemical reaction of submucosal injection solution, exposure to intra-gastric acid, or the electrocautery injury during pre-cutting and dissection. A low-level threshold for visceral pain due to gastric acid, also called acid hypersensitivity, could also

Table 3
Severity of post-ESD abdominal pain between the groups.

Group	BP (N=40)	Non-BP (N=43)	P
SF-MP Immediately after ESD	5.5±3.6	5.0±3.1	.541
Immediate abdominal pain after ESD	37 (92.5%)	41 (95.3%)	.934
VAS score	5.4±3.1	4.7±2.5	.301
Severity*			.549
Mild	11 (27.5%)	13 (30.2%)	
Moderate	13 (32.5%)	19 (44.2%)	
Severe	13 (32.5%)	9 (20.9%)	
SF-MP after 6 hours	4.2±3.7	4.1±2.6	.853
6 hours abdominal pain after ESD	35 (87.5%)	40 (93.0%)	.631
VAS score	3.8±2.5	3.4±1.8	.462
Severity			.301
Mild	16 (40.0%)	22 (51.2%)	
Moderate	13 (32.5%)	16 (37.2%)	
Severe	6 (15.0%)	2 (4.7%)	
SF-MP after 12 hours	2.5±2.3	2.5±1.8	.916
12 hours abdominal pain after ESD	33 (82.5%)	37 (86.0%)	.887
VAS score	2.4±1.8	2.3±1.4	.731
Severity			.401
Mild	24 (60.0%)	31 (72.1%)	
Moderate	7 (17.5%)	6 (14.0%)	
Severe	2 (5.0%)	0 (0.0%)	
Next-day SF-MP	1.6±1.9	1.5±1.4	.609
Next-day abdominal pain after ESD	28 (70.0%)	33 (76.7%)	.655
VAS score	1.5±1.7	1.5±1.2	.854
Severity			.400
Mild	24 (60.0%)	30 (69.8%)	
Moderate	2 (5.0%)	3 (7.0%)	
Severe	2 (5.0%)	0 (0.0%)	
Length of hospital stay, days, mean±SD	4.6±2.1	4.0±0.8	.127

ESD = endoscopic submucosal dissection, SF-MP = Short form McGill pain score, VAS = visual analogue scale.

* Severity was categorized as mild (VAS score is 1, 2, or 3), moderate (VAS score is 4, 5, or 6), and severe (VAS score is 7 or more).

contribute to the development of post-ESD abdominal pain. In this study, authors determined through multivariate analysis that the strongest risk factors for pain were tumor location in the lower third of the stomach (antrum and peripyloric area), baseline chronic dyspeptic symptoms, and no PPI administration. Notably, Ono et al showed that median intragastric pH in a pre-ESD treatment group (given PPI on the morning of ESD) was significantly higher than that in a group given PPI after the ESD procedure.^[21] Thus, PPI administration before ESD may prevent

Table 4
Factors associate with post-ESD abdominal pain using the univariate and multivariate logistic regression analysis.

Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Bupivacaine (non-BP vs BP)	1.90 (0.44–9.83)	.4003	0.35 (0.02–4.30)	.4131
Age (≥60 vs <60 yr)	0.36 (0.05–1.68)	.2300	0.20 (0.00–5.64)	.3577
Sex (Male vs Female)	0.34 (0.02–2.10)	.3316	0.14 (0.00–4.68)	.3065
BMI (≥ 30 vs <30)	0.50 (0.07–10.28)	.5518	0.01 (0.00–1.33)	.0870
Tumor size (≥20 vs <20 mm)	0.40 (0.06–1.87)	.2829	0.14 (0.00–2.66)	.2683
Procedure time (≤30 vs >30 min)	2.00 (0.43–14.28)	.4147	12.01 (0.46–852.69)	.1747
Coagulation time (≤ 5 vs >5 min)	2.77 (0.59–19.74)	.2300	1.39 (0.07–49.40)	.8316
En bloc resection (En bloc vs piecemeal resection)	1.33 (0.21–26.10)	.7963	0.04 (0.00–4.79)	.2955
Final pathology (EGC vs benign)	0.21 (0.03–0.98)	.0665	0.25 (0.02–2.71)	.2706

BMI = body mass index, BP = bupivacaine, CI = confidence interval, EGC = early gastric cancer.

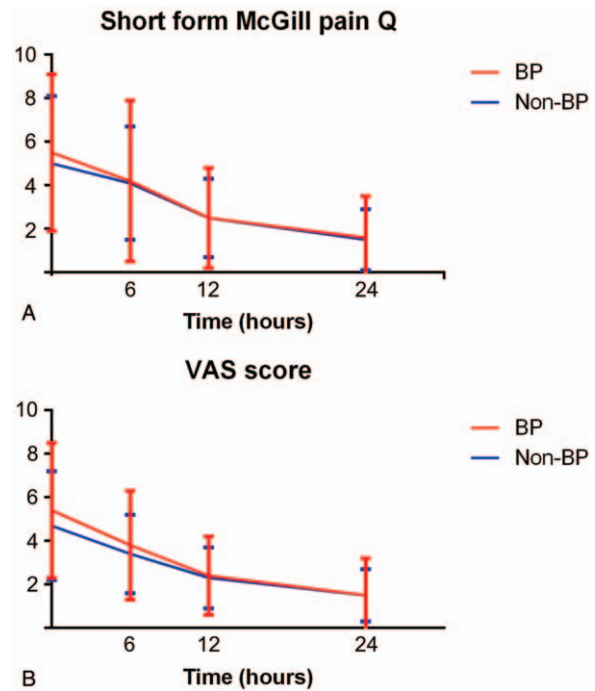


Figure 2. Total short-form McGill pain score and VAS score. The mean short-form McGill pain and VAS scores immediately after ESD were lower in the non-BP group than in the BP group, without significant difference. Furthermore, maximum pain was observed in patients of both groups immediately after ESD. VAS is visual analogue scale; BP is the bupivacaine group; non-BP is the conventional solution group; and ESD is endoscopic submucosal dissection. BP = bupivacaine, ESD = endoscopic submucosal dissection, VAS = visual analogue scale.

pain from developing after the procedure through acid suppression. In our study, endoscopists routinely administered PPI only after ESD, thus the timing of administration might have attributed to the negative results of our study.

An interesting finding of our study was that no factor was found significantly associated with post-ESD abdominal pain in patients. For example, in 47 patients with tumor size ≥20 mm, which is a well-known risk factor for post-ESD abdominal pain,^[3,20] there were no significant results in the multivariate logistic regression analysis. Additionally, regarding other possible risk factors such as procedure time^[7] or coagulation time,

univariate and multivariate logistic regression analysis did not show significant relation with post-ESD abdominal pain and administration of BP injection.

Another noteworthy result of our study was that maximum pain was observed in patients immediately after ESD, contrary to previous reports.^[3,8] Most studies reported that various pain scores were significantly higher at 6 hours after ESD than at other time points such as immediately, 12, or 24 hours after ESD. Even though the mechanism underlying higher intensity abdominal pain immediately after ESD compared with other time points is not clearly understood, it is attributed to CO₂ insufflation applied to all ESD procedures in our study. Recent studies^[22-24] demonstrated that CO₂ insufflation was superior to room air with regard to the pain score on the VAS in the hour after the endoscopic procedure. The mean pain score with time showed that patients had significantly higher pain scores 1-hour post-procedure. Thus, if ESD is performed with CO₂ insufflation, the time point with maximal pain score could be immediately or 1 hour after procedure instead of 6 hours or other time points.

Although our study is the first to evaluate the safety and efficacy of submucosal BP injection based on local anesthetic agents for visceral pain control, especially those targeting post-ESD abdominal pain, it has several limitations. First, the sample size in our study was relatively small. Thus, comparisons between groups may have limited reproducibility or generalizability. Furthermore, all procedures were performed by 4 different experienced endoscopists resulting in heterogeneity in the execution of the procedure leading to different degrees of submucosal layer trauma, which is another well-recognized risk factor for post-ESD abdominal pain. It is believed that ESD performed by endoscopists with different case volumes is associated with a different rate of abdominal pain, although enhanced case complexity in a referral center may diminish this effect. Other confounding factors that were not considered may have an effect on the incidence and severity of post-ESD abdominal pain.

In conclusion, the present study showed that BP does not reduce post-ESD abdominal pain in patients receiving a submucosal injection formula, and in subgroup analyses for high-risk groups. For this reason, further high-quality, comparative, large-scale, multicenter, randomized controlled trials of submucosal BP injection are needed to confirm our findings before final conclusions or recommendations can be made regarding its use for the prevention of post-ESD abdominal pain.

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