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Clinicopathological characteristics of patients with pain after endoscopic submucosal dissection for gastric epithelial neoplasm

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Abstract

Background Endoscopic submucosal dissection (ESD) is widely used for large superficial gastrointestinal tumors. Epigastric pain is a frequent complication of ESD. However, little is known about its incidence and associated factors. This study evaluated pain incidence and characteristics of patients with pain after gastric ESD.

Methods We retrospectively analyzed a prospectively collected registry of clinical, endoscopic, and pathologic results of patients who underwent ESD for gastric adenoma or cancer from January 2010 to December 2015. A Visual Analogue Scale (VAS) was used to assess pain immediately after, and 2, 12, and 24 h after ESD. The primary outcome was the use of painkillers (VAS score > 4). Analyzed data included age, sex, pathology, specimen and tumor size, procedure time, and tumor location.

Results Of 1226 patients, 461 (36.4%) needed a painkiller at least once after ESD (pain group). Compared with the no pain group, the pain group had more females, less alcohol consumption, larger tumor and specimen size, and more antral lesions. In multivariate analysis, female sex (OR 1.559, 95% CI 1.217–1.996, $p < 0.001$), antral tumor location (OR 1.780, 95% CI 1.398–2.265, $p < 0.001$), and procedure time over 30 min (OR 1.443, 95% CI 1.130–1.842, $p = 0.003$) were predictive factors for pain.

Conclusion This study showed that a considerable number of patients needed one or more painkiller doses after gastric ESD. The factors affecting pain included sex, procedure time, and lesion location. Endoscopists should use preemptive or aggressive pain management in high-risk patients after ESD.

Keywords Pain · Endoscopic submucosal dissection · Stomach · Complication

Recent advances in endoscopic techniques have enabled removal of gastric epithelial neoplasia easily and safely, even for large lesions or for those located in areas difficult to assess endoscopically. Endoscopic submucosal dissection (ESD) achieves en bloc and complete resection, regardless of lesion size [1]. Although ESD is an attractive method for treating gastric epithelial neoplasia in terms of therapeutic outcomes, as compared with endoscopic mucosal resection (EMR), it is associated with complication risks such as bleeding and perforation [2]. Many studies addressing these major complications have been performed [3, 4]. However, besides bleeding and perforation, other minor complications include stricture, pneumonia, fever, and pain [2]. Among these, pain is one of the most common complications. Although the majority of patients complain of abdominal pain after ESD [5], it tends to be relatively overlooked because it is not lethal. However, post-ESD pain is an important complication in terms of quality of life and health care costs [6, 7].

Post-procedural pain affects patient satisfaction with treatment, prolongs hospitalization, and increases healthcare costs. Although patients sign an informed consent form that describes minor pain without serious complications, many patients with post-procedural pain are concerned about whether the procedure was performed properly.

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Therefore, effective pain prevention and management may improve patient satisfaction and compliance with additional treatment or surveillance. A patient who experiences post-ESD pain may fear a subsequent endoscopic procedure for metachronous or recurrent lesions. As ESD is organ-sparing, metachronous lesions are an important issue in surveillance [8]. Therefore, repeat ESD is common, even in patients who undergo curative resection [8]. Naturally, management of post-ESD pain is important in terms of patient compliance.

A few small studies have reported various incidence rates of post-ESD pain [5, 9, 10]. Choi et al. demonstrated that almost all patients (98%) felt pain after ESD, regardless of pain severity [5]. A recent study showed that 66 (42.3%) of 156 patients who underwent endoscopic resection for gastric tumor received intravenous pethidine due to abdominal pain after the procedure [9]. Owing to the small sample size or heterogeneity of study populations, previous studies were underpowered for explanation of the incidence of post-ESD pain.

Furthermore, it is unclear which patients experience more frequent or severe pain after ESD. Although not fully understood, abdominal pain following ESD may be caused by residual mucosal defects, transmural air leaks, thermal electric burns, and/or hypersensitivity to acid [10–13]. Based on these mechanisms, some investigators have attempted to reduce the pain that develops after ESD [14–16]. Recently, Jung et al. have suggested that hypersensitivity to acid might be associated with post-ESD pain [10]. They also demonstrated that prophylactic proton-pump inhibitor (PPI) treatment was effective at reducing pain [10]. A recent small study demonstrated that female sex, tumor location, and procedure time were significantly associated with pain after, both EMR and ESD [9]. However, few studies have identified the factors affecting pain after ESD. A proper investigation of the incidence and risk factors would help in the management and prevention of post-ESD pain.

With this background, this study aimed to explore, both the incidence of pain following gastric ESD and clinicopathologic factors associated with pain in a large number of patients.

Methods

Patients

From January 2010 to December 2015, we prospectively collected a registry (KHU-ESD registry) of clinical, endoscopic, and pathologic results in patients who underwent ESD for gastric adenoma or cancer at a tertiary teaching hospital (Kyung Hee University Hospital, Seoul, Korea). The database was updated by gastroenterologists using a standardized reporting system. Patient demographic data, procedure-related data, pathologic results, use of medications such as antiplatelet agents, and complications including perforation, bleeding, and pneumonia were recorded. In this analysis, patients with multiple lesions, those taking a painkiller on admission, those with major complications such as perforation and bleeding, and those with failed ESD were excluded. The study was approved by the Institutional Review Board of Kyung Hee University Hospital (KMC IRB 1410-08).

ESD procedure

Prior to the endoscopic procedure, written informed consent was obtained from all patients. All patients received anticholinergics intravenously (IV) as premedication. The patients were initially sedated with an IV bolus of midazolam (0.05–1 mg/kg) and propofol (0.5 mg/kg). Sedation was maintained with repeated doses of 10–20 mg propofol. The target level was deep sedation based on the American Society of Anesthesiologists system [17]. According to standard ESD procedure, all procedures were performed by a single experienced endoscopist (J.Y. Jang), using an endoscope with a water-jet system (GIF-Q260J or GIF-2TQ260M; Olympus, Tokyo, Japan) and room air insufflation. The ESD procedure consisted of marking the lesion, incision, submucosal dissection, and hemostasis. First, the lesion was marked 5 mm outside the external margin using argon plasma coagulation (ERBE, Tubingen, Germany). Then, a mixed solution of glycerin, epinephrine, and indigo carmine was injected into the marked submucosa. Incisions were made external to the lifted lesion using a needle knife (KD-V451 M, Olympus Medical Systems Co., Ltd., Tokyo, Japan) or IT knife2 (KD-611L, Olympus Medical Systems), followed by dissection of the submucosal layer. During the dissection, a mixture of solutions was injected repeatedly into the submucosal layer to maintain lifting of the lesion. During and after completion of dissection, hemostasis and ablation of non-bleeding visible vessels were achieved using hemostatic forceps (Coagrasper FD-410LR; Olympus). VIO 300D (ERBE) was used as the electrosurgical unit. After the procedure, all patients received intravenous esomeprazole (Nexium; AstraZeneca Korea, Seoul, Korea), with an 80-mg loading dose over 5 min, followed by intravenous infusion at 8 mg/h for 24 h. After completion of IV infusion, patients received a standard dose of oral PPI and were discharged on the second day after ESD.

Evaluation of outcomes

We only investigated pain that might be associated with ESD; subsets included epigastric pain, abdominal pain, abdominal distension, and back pain. A Visual Analogue Scale (VAS) score was used to assess pain immediately

after, and 2, 12, and 24 h after the procedure. Patients were advised that the score required for drug intervention was > 4. As individual patient VAS scores indicating need for pain intervention varied, we proposed a score of > 4 as a reference. If the patient wanted pain control for severe pain exceeding VAS score 4, 50 mg of IV tramadol was preferentially administered and repeated as needed. If a patient needed additional painkillers despite IV tramadol, pethidine was given once intramuscularly. Patients who still had pain after the first pethidine injection were given a repeat dose. According to our management protocol, all patients received an abdominal X-ray, 2 h after ESD. However, patients with abdominal pain underwent X-ray or computed tomography after a thorough physical examination by a physician, whenever perforation was suspected. The primary outcome was the use of painkillers such as tramadol or pethidine. According to the use of painkillers (pain group vs. no pain group), analyzed data included age, sex, smoking, alcohol consumption, presence of *Helicobacter pylori* infection, histology, specimen and tumor size, procedure time, and lesion location (cardia, body, or antrum). Total procedure time was defined from the start of circumferential marking around the lesion to completion of the overall ESD procedure. Dissection time was defined from the start of marking to completion of dissection. Coagulation time was defined from the end of dissection to complete hemostasis after dissection.

Statistical analysis

Continuous variables were compared using Student's *t* test for parametric data or the Mann–Whitney U test for nonparametric data. Categorical variables were compared using the Chi square test or Fisher's exact test. All statistical analyses were performed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA). Risk factors for post-ESD pain were subjected to logistic regression analysis. All statistical tests were two-tailed, and a p value of < 0.05 was considered statistically significant.

Results

During the study period, 1431 eligible patients who underwent ESD for gastric adenoma or carcinoma were recruited. After 165 patients were excluded because of multiple lesions (53), incomplete data (78), discharge within 24 h (12), prior use of painkillers (3), failed ESD (6), post-ESD bleeding (10), aspiration pneumonia (2), and fever of unknown cause (1), 1266 patients were finally analyzed (Fig. 1).

Patient clinicopathologic characteristics are shown in Table 1. Mean age was 64.4 ± 9.7 years old, and 873 patients (69.0%) were male. The lesions were mainly located in the antrum (52.1%) and lesser curvature (39.3%) of the stomach. Mean size of the tumor and resected

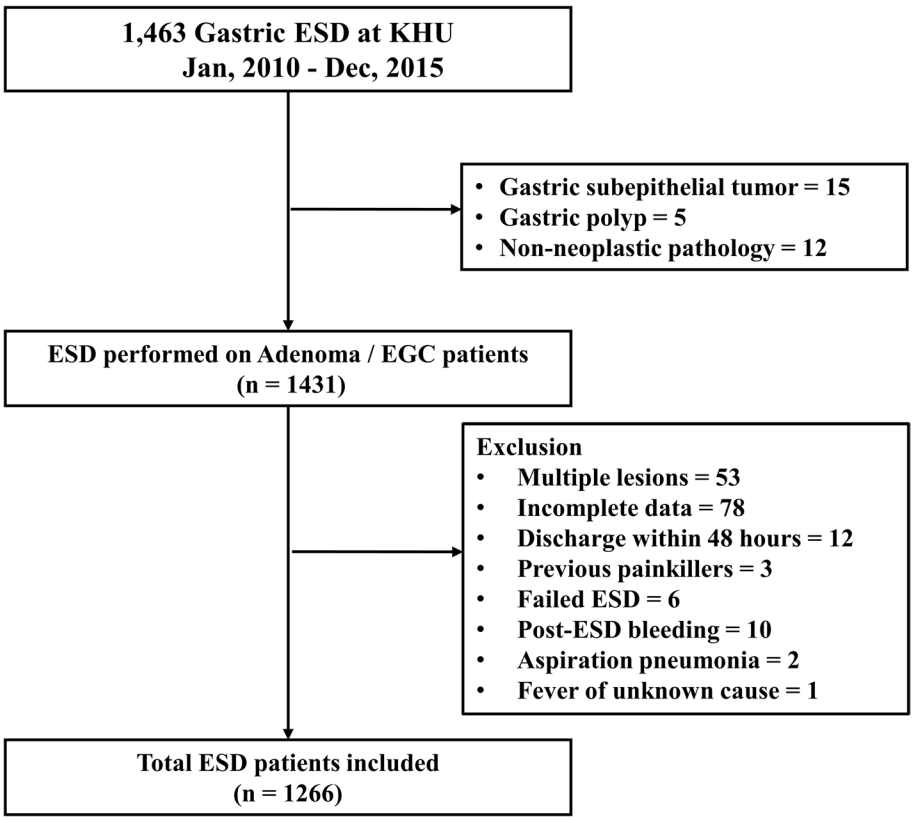

Fig. 1 Flow diagram of the study

Table 1 The clinicopathological characteristics of enrolled patients

Characteristics	Value
Total no. of patients	1266
Age (mean ± SD, year)	64.4 ± 9.7
Gender (male, %)	873 (69.0)
Smoking	230 (18.2)
Alcohol	571 (45.1)
BMI	24.5 ± 3.2
Tumor size (mean ± SD, mm)	16.1 ± 12.9
Resection size (mean ± SD, mm)	39.7 ± 14.7
Location	
Cardia	37 (2.9)
Body	569 (44.9)
Antrum	660 (52.1)
Histology	
Adenoma	694 (54.8)
Carcinoma	572 (45.2)
Histological depth	
Mucosa	1141 (90.1)
Submucosa	125 (9.9)
Procedure time	
Total procedure time (mean ± SD, min)	39.6 ± 29.0
Dissection time (mean ± SD, min)	33.1 ± 26.0
Coagulation time (mean ± SD, min)	6.5 ± 5.1
H. pylori infection	618 (48.8)

SD standard deviation, *BMI* body mass index

specimen were 16.1 ± 12.9 and 39.7 ± 14.7 mm, respectively. In final pathology, adenoma including low- and high-grade dysplasia accounted for slightly more than half (54.8%). Among 572 patients with carcinoma, 125 (21.9%) had submucosal invasion. Of the mean 39.6 ± 29.0 min total procedure time, 6.5 ± 5.1 min accounted for coagulation time.

Among 1266 enrolled patients, 461 (36.4%) received painkillers one or more times due to abdominal pain after the procedure. These patients were classified in the pain group. Patient clinical characteristics are summarized in Table 2. There was no difference in age between the pain group and no pain group ($p = 0.604$). However, the proportion of males and alcohol consumers was significantly higher in the no pain group. Both tumor and resected specimen sizes were significantly larger in the pain group (15.5 ± 11.6 vs. 17.1 ± 14.8 and 39.0 ± 13.8 vs. 41.3 ± 16.0 mm, respectively). There was no difference in either the histology or depth of invasion between the two groups. In the pain group, lesions were significantly more frequently located in the antrum (60.1 vs. 47.6%, $p < 0.001$). Total procedure times in the pain group were longer than in the no pain group (41.6 ± 31.5 vs. 38.5 ± 27.4 min, $p = 0.074$), as were dissection (34.8 ± 28.2 vs. 32.2 ± 24.6, $p = 0.083$) and coagulation (6.8 ± 5.2 vs. 6.4 ± 5.1, $p = 0.291$) times, but the differences did not reach statistical significance.

More detailed distribution of tumor within the antrum is shown in Table 3. In 660 patients with tumor located in the antrum, 277 (42.0%) were included in the pain group. In the pain group, tumors were more frequently located in the distal antrum without reaching statistical significance (44.0 vs. 37.1%, $p = 0.071$). Anterior wall (AW) location (28.2 vs. 19.1%, $p = 0.006$) was more common and greater curvature (GC) location (18.1 vs. 30.8%, $p < 0.001$) was less common in the pain group. In combined longitudinal and circumferential location, AW in the proximal antrum was significantly more common in the pain group (16.2 vs. 11.0%, $p = 0.048$), with GC location less common in the no pain group (10.1 vs. 24.3%, $p < 0.001$).

The trend of the VAS score for the 24 h after the procedure is shown in Table 4 and Fig. 2. At all time points, scores were significantly higher in the pain group (all $p < 0.001$). However, the score differences decreased over time (Fig. 2). In logistic regression analysis, female sex (odds ratio [OR] 1.559, 95% confidence interval [CI] 1.217–1.996), antral tumor location (OR 1.780, 95% CI 1.398–2.265), and total procedure time longer than 30 min (OR 1.443, 95% CI 1.130–1.842) were significantly associated with post-ESD pain (Table 5). However, there was no association with age, alcohol consumption, or tumor and specimen size.

Discussion

This study showed that 461 (36.4%) of 1266 patients who underwent gastric ESD needed a painkiller for abdominal pain after the procedure. This finding suggested that endoscopists should be more aware of post-ESD pain to improve patient satisfaction. Furthermore, our results demonstrated that female sex, total procedure time, and antral tumor location were predictive of post-ESD pain. Thus, to reduce or prevent pain, patients with these factors should be proactively managed with preemptive medication or adjustment of modifiable risk factors such as procedure time.

Pain after ESD is a very common non-lethal complication, and thus has been taken for granted by endoscopists. With expansion of ESD indications for treatment of early gastrointestinal cancers or premalignant lesions, endoscopists should take more interest in patient quality of life. Although post-ESD pain is generally transient and self-limited, it is common, and is a critical factor affecting quality of life and health care costs [6, 7]. Some previous studies reported an incidence of 42.3–98% [5, 9]. Jung et al. reported that the incidence of moderate to severe post-ESD pain requiring painkillers was 53.8% [10]. The present study showed that 36.4% of patients who underwent ESD needed a painkiller one or more times after the procedure. This is somewhat

Table 2 Comparison of clinical characteristics according to the pain

	Pain ($n=461$)	No pain ($n=805$)	p value
Total no. of patients, *n* (%)	461 (36.4)	805 (63.6)	
Age (mean ± SD, year)	64.2 ± 10.0	64.5 ± 9.5	0.604
Gender (male, %)	290 (62.9)	583 (72.4)	< 0.001
Smoking, *n* (%)	83 (18.0)	147 (18.3)	0.909
Alcohol, *n* (%)	186 (40.3)	385 (47.8)	0.010
BMI	24.6 ± 3.4	24.4 ± 3.1	0.196
Tumor size (mean ± SD, mm)	17.1 ± 14.8	15.5 ± 11.6	0.041
Resection size (mean ± SD, mm)	41.3 ± 16.0	39.0 ± 13.8	0.010
Histology			0.254
Adenoma, *n* (%)	243 (52.7)	451 (56.0)	
Cancer, *n* (%)	218 (47.3)	354 (44.0)	
Location			< 0.001
Cardia, *n* (%)	9 (2.0)	28 (3.5)	
Body, *n* (%)	175 (38.0)	394 (48.9)	
Antrum, *n* (%)	277 (60.1)	383 (47.6)	
Histological depth			0.491
Mucosal, *n* (%)	419 (90.9)	722 (89.7)	
SM invasion, *n* (%)	42 (9.1)	83 (10.3)	
Procedure time			
Total procedure time (mean ± SD, min)	41.6 ± 31.5	38.5 ± 27.4	0.074
Dissection time (mean ± SD, min)	34.8 ± 28.2	32.2 ± 24.6	0.083
Coagulation time (mean ± SD, min)	6.8 ± 5.2	6.4 ± 5.1	0.156
H. pylori infection, *n* (%)	216 (46.9)	402 (49.9)	0.291

Table 3 Distribution of location in patients with tumor in the antrum

	Pain	No pain	p value
Total no. of patients, *n* (%)	277 (42.0)	383 (58.0)	
Antral location I			0.071
Proximal, *n* (%)	155 (56.0)	241 (62.9)	
Distal, *n* (%)	122 (44.0)	142 (37.1)	
Antral location II			
AW	78 (28.2)	73 (19.1)	0.006
GC	50 (18.1)	118 (30.8)	< 0.001
PW	52 (18.8)	73 (19.1)	0.926
LC	97 (35.0)	119 (31.1)	0.286
Antral location III			
Proximal + AW	45 (16.2)	42 (11.0)	0.048
Proximal + GC	28 (10.1)	93 (24.3)	< 0.001
Proximal + PW	31 (11.2)	35 (9.1)	0.386
Proximal + LC	51 (18.4)	71 (18.5)	0.967
Distal + AW	33 (11.9)	31 (8.1)	0.102
Distal + GC	22 (7.9)	25 (6.5)	0.485
Distal + PW	21 (7.6)	38 (9.9)	0.298
Distal + LC	46 (16.6)	48 (12.5)	0.139

AW anterior wall, *GC* greater curvature, *PW* posterior wall, *LC* lesser curvature

less than reported in previous studies. Female sex, longer procedure time, and acid hypersensitivity are potential risk factors for post-ESD pain suggested by previous studies [9, 10]. Therefore, the male predominance of the study population and shorter procedure times than previously reported may have resulted in a lower incidence of post-ESD pain [9, 10]. Another possible explanation is that all patients in the present study were given a high PPI dose for the first 24 h after ESD, when pain is greatest.

Although not fully understood, several mechanisms by which pain develops after ESD have been suggested. Some studies demonstrated that transmural burns and air leaks were associated with post-ESD pain [11, 12]. A recent study using an acid infusion test suggested that acid hypersensitivity was one mechanism of post-ESD pain [10]. A severe inflammatory reaction [18] and contraction of inflamed tissue [10] may also be mechanisms of pain development, as can bile acid regurgitation [19] and gas distension [9] after ESD. Based on these mechanisms, several researchers investigated ways to relieve pain after ESD. Topical [14] and systemic steroids [15] were used to reduce pain associated with inflammation. Some studies tried to relieve pain using analgesics such as lidocaine [16] or a transdermal fentanyl patch [5] during or after ESD. By preventing acid hypersensitivity, Jung et al. demonstrated

Table 4 The trend of the VAS score according to the time in the both group

Group	0 h*	2 h*	12 h*	24 h*	Maximum*
Overall ($n=1266$)	1.7 ± 2.4	1.0 ± 1.9	0.8 ± 1.6	0.2 ± 1.0	2.5 ± 2.5
Pain ($n=461$)	3.5 ± 2.8	2.2 ± 2.5	1.7 ± 2.1	0.6 ± 1.5	5.0 ± 2.0
No pain (−) ($n=805$)	0.6 ± 1.2	0.4 ± 0.9	0.3 ± 0.8	0.1 ± 0.4	1.0 ± 1.4

*Differences of VAS score at all time points were statistically significant between the groups ($p<0.05$)

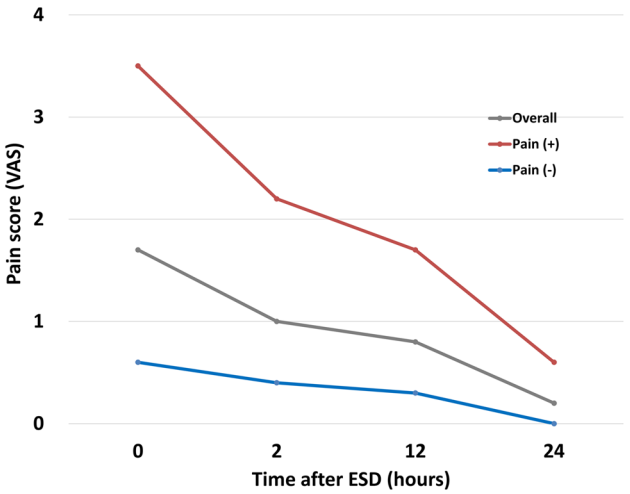

Fig. 2 The change of pain intensity after endoscopic submucosal dissection

Table 5 Logistic regression model for the predictors of pain after endoscopic submucosal dissection

	OR	95% CI	*p* value
Age (> 60)	1.078	0.840–1.383	0.558
Female	1.559	1.217–1.996	< 0.001
Alcohol	0.853	0.674–1.080	0.187
Tumor size (> 20 mm)	1.088	0.718–1.648	0.692
Specimen size (> 40 mm)	1.149	0.889–1.483	0.289
Location (antrum)	1.780	1.398–2.265	< 0.001
Total procedure time (> 30 min)	1.443	1.130–1.842	0.003

OR odds ratio, *CI* confidence interval

that prophylactic PPI treatment can reduce post-ESD pain [10]. Therefore, high-dose PPI treatment during the first 24 h after ESD in the present study may have resulted in a lower frequency of post-ESD pain compared with previous studies. Although we did not directly evaluate mechanisms of pain development, our identification of predictive factors including female sex, longer procedure time, and antral tumor location may have confirmed previous hypotheses. Moreover, acid hypersensitivity was also identified as a potential predictive factor, as inferred by decreased pain development in patients using the high-dose PPI administration protocol in this study.

However, few studies had evaluated the predictive factors for post-ESD pain. Uehara et al. [20] demonstrated that the incidence of upper abdominal pain after ESD was significantly higher in patients whose tumor was located in the antrum or pylorus. Kim et al. [14] also identified fibrosis and size of residual ulcer as independent risk factors for pain in 111 patients with early gastric cancer. More recently, Kim et al. [9] analyzed 156 patients who underwent endoscopic resection to identify predictive factors for pain. They found that female sex, tumor location in the lower third of the stomach, and longer procedure time (≥ 60 min) were significantly associated with pain. Our study showed similar results in the analysis of a large number of patients. We found that predictive factors for post-ESD pain included female sex, antral tumor location, and total procedure time over 30 min. It was not surprising that females had greater pain sensitivity, due to differences in central visceral nociceptive pathways, hypervigilance, and the degree of anxiety [21]. Physiologically, gastric contraction is mainly performed by the antrum to expel the gastric contents [22]. After ESD, peristalsis in an ulcerated and inflamed antrum due to dissection and coagulation may result in more intense pain than in other parts of the stomach [10]. Moreover, tumor location in the distal antrum near the pylorus was more common in the pain group, with borderline significance in the present study. This finding suggested the possibility that regurgitated bile acid may play a role in pain development [19]. Longer procedure time is determined by several factors, including the endoscopist's skill, location and size of the lesion, submucosal fibrosis, and patient cooperation during the procedure. The longer time can result in a large amount of gas instillation and a severe electrical burn that may induce more pain, as suggested in previous studies [18].

As noted, the present and several other studies consistently demonstrated certain risk factors for post-ESD pain. In patients with such risk factors, preemptive management or prevention can reduce post-ESD pain. For example, endoscopists should attempt to reduce procedure time through improvement of skills and optimal use of endoscopy instruments. Compared with surgery, repetitive ESD procedures are more likely to be performed for metachronous lesions, as ESD spares more of the gastric mucosa [8]. Patients who experience pain after ESD may fear a subsequent procedure, resulting in poor compliance. Despite the potential effects of post-ESD pain, no study has examined

these issues. Therefore, we believe that further studies are needed to evaluate the impact of post-ESD pain on quality of life, health care costs, and patient compliance.

Our study has several strengths. First, this evaluation of post-ESD pain is the largest study reported to date. Although this was a descriptive study, our results demonstrated the incidence and predictive factors for post-ESD pain requiring painkillers through the analysis of a large study population. Second, all procedures in this study were performed by an experienced endoscopist, with use of the same pre- and post-procedural management protocol. The study minimized bias from technical factors such as the types of knives used, electrosurgical unit settings, and procedural skills. Thus, the study population was homogeneous. As we only used midazolam and propofol for sedation without analgesic effect, we were able to evaluate pure ESD-induced pain.

This study also had limitations. First, the definition of pain was somewhat ambiguous and was only defined as a need for painkillers, regardless of the cause of pain or numeric intensity score. We only used the VAS scale to assess the degree of pain, but this may accurately reflect the need for painkillers in actual clinical practice. Second, the generalizability of this study may be limited, as a single endoscopist in a university hospital performed all ESD procedures. Thus, further multicenter studies are required to determine the reproducibility of our results in other hospital settings. Next, technical factors during the procedure, including endoscopist proficiency, types of knives used, and electrosurgical unit settings, were not evaluated as risk factors. Further studies are warranted because these technical factors may affect pain.

In conclusion, our data showed that many patients who underwent ESD for gastric epithelial neoplasms needed one or more painkiller doses after the procedure. Furthermore, we identified factors affecting pain, including female sex, procedure time, and lesion location. These results suggested that endoscopists should be aware of post-ESD pain and should use preemptive or aggressive management, especially in patients with risk factors.

Compliance with ethical standards

Disclosures Jung-Wook Kim, Jae-Young Jang, Yoo Min Park, Jae-Jun Shim, and Young Woon Chang have no conflicts of interest or financial ties to disclose

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