Original Article

A Novel One-Step Knife Approach Can Reduce the Submucosal Injection Time of Endoscopic Submucosal Dissection: A Single-Blinded Randomized Multicenter Clinical Trials

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Background/Aims: Endoscopic submucosal dissection (ESD) is a curative treatment modality for early gastric neoplasms; however, ESD can be a time-consuming process. To overcome this pitfall, we developed the one-step knife (OSK) approach, which combines an endoscopic knife and injection needle on a single sheath. We aimed to evaluate whether this approach could reduce the ESD procedure time.

Methods: This single-blinded randomized multicenter trial at four tertiary hospitals from June 2019 to June 2020 included patients aged 19 to 85 years undergoing ESD. Patients were randomly assigned to two groups (OSK or conventional knife [CK]). The injection time, total procedure time, resected specimen size, submucosal fluid amount, degree of device satisfaction, and adverse events were evaluated and compared between groups.

Results: Fifty-one patients were analyzed (OSK: 25 patients and CK: 26 patients). No baseline differences were observed between groups, with the exception of a higher portion of males in the OSK group. The mean injection time was significantly reduced in the OSK group (39.0 seconds) compared to that in the CK group (87.5 seconds, p<0.001). A decrease of more than 10 minutes in the total procedure time (18.0 minutes vs 28.1 minutes, p=0.055) in the OSK group compared to the CK group was observed. Second-look esophagogastroduodenoscopy revealed two delayed bleeding cases in the OSK group that were easily controlled by endoscopic hemostasis.

Conclusions: OSK reduced the injection time and showed a decrease in total procedure time compared with the CK approach. OSK can be a feasible tool for ESD, especially in difficult cases. **(Gut Liver 2022;16:44-52)**

Key Words: Gastric cancer; Endoscopic submucosal dissection; Submucosal injection; Procedure time

INTRODUCTION

Stomach cancer is the second most common cancer among all malignancies in Korea.[1] Since 1999, the Korean National Cancer Screening Program has recommended esophagogastroduodenoscopy or upper barium radiologic testing as gastric cancer screening to the general population over the age of 40 years. As a result, over 70% of stomach cancers have been detected as early gastric cancer (EGC).[2,3] Since its introduction in the early 2000s, endoscopic submucosal dissection (ESD) has provided many advantages in terms of quality of life and short- and long-term clinical outcomes.[4-7] Currently, ESD has been accepted as a curative treatment modality for EGC or gastric adenoma with a steady increase in cases of up to 6,000 per year for EGC and over 23,000 per year for early gastric neoplasms.[7]

The ESD procedure includes marking around the lesion, submucosal injection, mucosal incision, and submucosal dissection. Among these steps, submucosal injection is an essential process that prevents perforation during mucosal incision and provides the submucosal dissection area; usually more than two submucosal injections are needed during a single ESD procedure. However, submucosal injection is a bothersome and time-consuming process that includes inevitable subprocesses such as endoscopic knife withdrawal, needle injector insertion, submucosal fluid injection, needle injector withdrawal, and endoscopic knife insertion. This process requires more than 1 minute per submucosal injection. When many subsequent submucosal injections are required, the procedural time may be substantially prolonged.

Prolonged ESD procedural time is associated with adverse events such as perforation, aspiration pneumonia, and post-ESD bleeding.[8,9] Nevertheless, because some fixed parameters determine the ESD procedural time (e.g., endoscopist skill, lesion size and location, and rounds of submucosal injection),[10-12] shortening the ESD procedure is not feasible using the conventional approach.

To overcome this, we developed a novel hybrid knife-injector complex that operates similarly to using a multicolor ballpoint pen. In a preclinical animal model test, the hybrid knife-injector complex (one-step knife [OSK]; Upexmed, Anyang, Korea) showed a marked reduction of submucosal injection time.

To investigate the OSK approach in humans, we conducted a multicenter trial to evaluate whether OSK can reduce the submucosal injection time in humans and whether reducing the submucosal injection time by OSK can effectively reduce the total ESD procedure time.

MATERIALS AND METHODS

This was a single-blinded (participants) randomized multicenter trial with a parallel design including a 1:1 allocation ratio among four participating tertiary hospitals. This study was approved by the Institutional Review Board in Wonju Severance Christian Hospital (IRB number: CR218006) and was registered on clinical research information service (CRIS number: KCT0004046).

1. Study population

Among patients aged 19 to 85 years who had planned to undergo ESD for EGC or gastric adenoma, the patients who agreed and submitted informed consent were enrolled. We excluded patients with serious cardiopulmonary disease, coagulation disorder, and who underwent gastrectomy.

Patients were randomly assigned to either the OSK group or the conventional knife (CK) group according to a computer-generated random table with stratification of the stomach site to the body and antrum. Central allocation by telephone was used to conceal allocation.

2. Procedures and intervention

A total of seven endoscopists participated in this study who have experience of ESD more than 500 cases. Before the clinical trial, all endoscopists and assistants underwent an OSK operation training period using an animal model (pig stomach).

All patients underwent ESD under sedation. A standard scope (HQ290 or Q260) was used for all ESDs. After careful demarcation with white light endoscopy, indigo carmine, and narrow-band imaging, a marking around lesion was made with a knife or argon plasma coagulation.

In the OSK group, submucosal injection, mucosal incision, and submucosal dissection were performed using only an OSK. In the CK group, submucosal injection with needle injector, incision, and dissection were performed with a CK. The submucosal injection fluid was composed of 7 mL normal saline with 1 mL epinephrine (1:100,000). Injection times using a stopwatch and the amount of injection were recorded. Before finishing ESD, preventive hemostasis with hemoclips or coagrasper was done. After ESD, endoscopists and assistants filled out satisfaction questionnaires of the devices. The next day, a second-look endoscopy was performed to check for delayed bleeding.

3. Device (OSK)

From 2016, we developed a complex device containing a knife and needle injector comprised into one sheath. The technical development difficulties consisted of mainly three parts: (1) smooth switchover under the extremely bending situation of endoscopy; (2) simple operation handle switch to facilitate the switchover; and (3) same quality of knife tip as the CK (dual knife). After many revisions, the technical problems were resolved and we performed a clinical trial with our final product (Fig. 1).

The OSK contains two instruments (endoscopic knife and needle injector) in one channel. The endoscopic knife is identical to the dual knife (Olympus, Tokyo, Japan), which has a 2-mm knife tip. A 25-gauge needle injector of the OSK is sufficient for epinephrine mixed normal saline injection as well as hyaluronic acid mixed fluid injection. The switchover to knife or needle injector is made by a handle switch that includes a gear structure conversion mechanism (Fig. 2). An assistant can switchover between the two instruments without removing an electrode linked with the endoscopic surgical generating unit (ESU). In
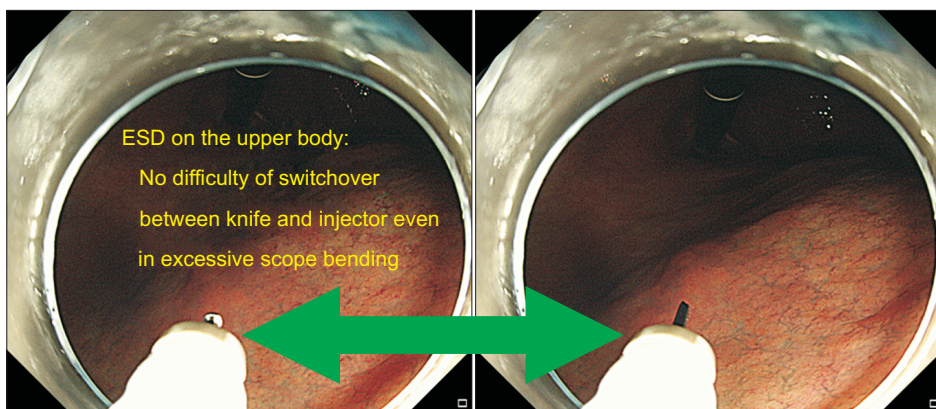
ESD on the upper body:
No difficulty of switchover
between knife and injector even
in excessive scope bending

Fig. 1. Smooth switchover of one-step knife under the extreme bending situation of endoscopy. ESD, endoscopic submucosal dissection.

Neutral position
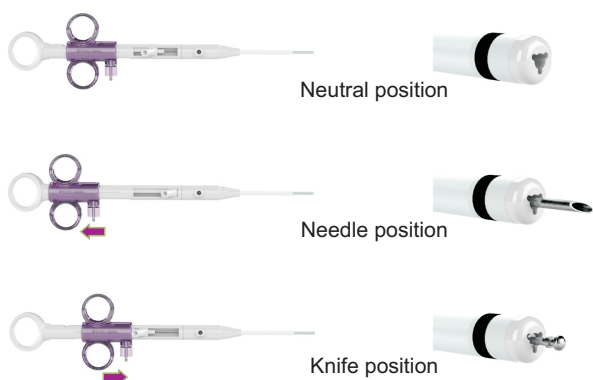
Needle position

Knife position

Fig. 2. The one-step knife has single channel which the endoscopic knife and needle injector pass through alternatively. The switchover between the knife and needle injector is made by a handle switch.

Korea, the dual knife or IT knife 2 are mainly used. So, we compared OSK with dual knife in point of knife efficacy. We used ESU (Erbe Vio300; Erbe Elektromedizin GmbH, Tübingen, Germany) with Endo cut Q mode.

4. Outcomes and definitions

The primary outcomes were injection time and total procedure time. The secondary outcomes were (1) *en bloc* resection; (2) resected specimen size; (3) submucosal fluid amount; (4) delayed bleeding and delayed perforation; (5) endoscopist satisfaction; and (6) assistant satisfaction.

We defined the injection time as the time from the "endoscopic knife out" for submucosal injection followed by the "endoscopic knife in" in the CK group and the time from switchover (from knife to injector) for submucosal injection followed by switchover (from injector to knife) in the OSK group. The time of the first marking to the time of falling off the specimen was defined as the total procedure time. To reduce bias, we determined the target lesion size to be 2–3 cm and to be without fibrosis. Stomach location could be an important factor for total procedure time; thus, we stratified the site of lesion which defined the

body as the upper site and the angle to antrum as the lower site. The device satisfaction questionnaire administered to endoscopists and assistants included questions regarding overall satisfaction, overall satisfaction of the procedural process, and overall satisfaction of submucosal injection. We adopted a 5-point satisfaction scale: (1) very satisfactory, (2) satisfactory, (3) not so satisfactory, (4) dissatisfactory, and (5) very dissatisfactory.

5. Sample size and statistical analysis

This study was designed as a superiority test, and the independent variable was the type of knife. We defined the alpha: 0.05, beta: 0.20, power: 0.80, and two tail, allocation ratio N2/N1: 1. Based on previous animal testing in pig stomachs, we assumed the mean injection time in the OSK group to be 40 seconds, and the mean injection time in the CK group to be 60 seconds with a standard deviation of 25 seconds. The effect size(s) was 0.8. As a result, the sample size was 22 patients per group, with a total of 44 patients in both groups. The follow-up loss rate was assumed as 20%; thus, a total of 56 patients were calculated (each hospital: seven patients in the CK group, seven patients in the OSK group). We did not perform interim analysis.

Continuous data are expressed as medians with ranges or standard deviations; categorical parameters are expressed as frequencies and proportions. For continuous data, test of normality was performed using the Shapiro-Wilk test; non-parametric variables were compared using the Mann-Whitney U test and the parametric variables were compared using the independent t-test. Categorical parameters were compared using the chi-square test or Fisher exact test. Multiple regression for procedure time was performed after age, sex, injection number, and maximal diameter were adjusted. All p-values were two-sided and were considered statistically significant if $p < 0.05$. All statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

From June 2019 to June 2020, 98 patients were screened; 42 patients were excluded for the following reasons: age >85 years (n=13), previous gastrectomy (n=3), lesions over 3 cm or with fibrosis (n=17), and declined participation (n=9). A total of 56 patients were randomized to the OSK (n=28) or CK (n=28) groups. Among them, a total of 51 patients were ultimately analyzed except for four patients who refused the scheduled ESD (two OSK and two CK) and one patient who did not undergo the OSK approach because of an ESU error (Fig. 3).

1. Baseline characteristics and procedural data

Baseline characteristics were not significantly different between the OSK and CK groups, with the exception of a higher proportion of males in the OSK group than in the CK group (92.0% vs 61.5%, p=0.010).

All patients underwent ESD under sedation. The proportions of patients receiving midazolam, propofol and pethidine were not different between the OSK and CK groups. The most common lesion morphologies were type 0-II (IIa, IIb, IIc). No significant difference in morphology between the two groups were noted. All lesions were *en bloc* resected. The most common histologic diagnosis before ESD was low-grade dysplasia in both groups (p=0.090) (Table 1).

2. Injection time, total procedure time

There was a significant difference in the mean injection time between the OSK and CK groups (mean, 39.0 seconds; range, 26.5 to 59.5 seconds and mean, 87.5 seconds; range, 75.0 to 99.3 seconds, respectively, p<0.001). In addition, a reducing trend of more than 10 minutes in the OSK group compared to that in the CK group was observed in

the total procedure time (mean, 18.0 minutes; range, 16.5 to 29.5 minutes and mean, 28.1 minutes; range, 18.0 to 39.6 minutes, respectively, p=0.055). In contrast, there were no significant differences in injection number (p=0.723) and maximal diameter (p=0.280). The total injection amounts and injection amount per one injection were significantly lower in the OSK group than in the CK group (p=0.029, p=0.007, respectively) (Table 2, Fig. 4).

Multiple linear regression analysis was performed using age, sex, lesion size and knife. When examining the effect of the above variables on the procedure time, the R square value was 0.226 and analysis of variance was p=0.005. The range of variance inflation factor were 1.028 to 1.372. The standardized coefficients betas were 0.359 on site, 0.353 on maximal diameter, and 0.269 on kind of knives, which means the procedure time is influenced by site of lesion, size of lesion and kind of knives.

3. Subgroup analysis

The median injection number was three per ESD; thus, we divided cases into low frequency injection (1 to 3 times) and high frequency injection (4 or more times) groups. Subgroup analysis revealed a statistically significant difference in total procedure time for the high but not the low frequency injection group (p=0.044, p=0.293, respectively) (Table 3, Fig. 5).

4. Satisfaction and complications

Regarding responses to the questionnaire, endoscopists rather than assistants yielded a very satisfactory trend in device satisfaction. Endoscopists gave a statistically significant response that the OSK was very satisfactory, especially in submucosal injection (p=0.009) (Table 4).

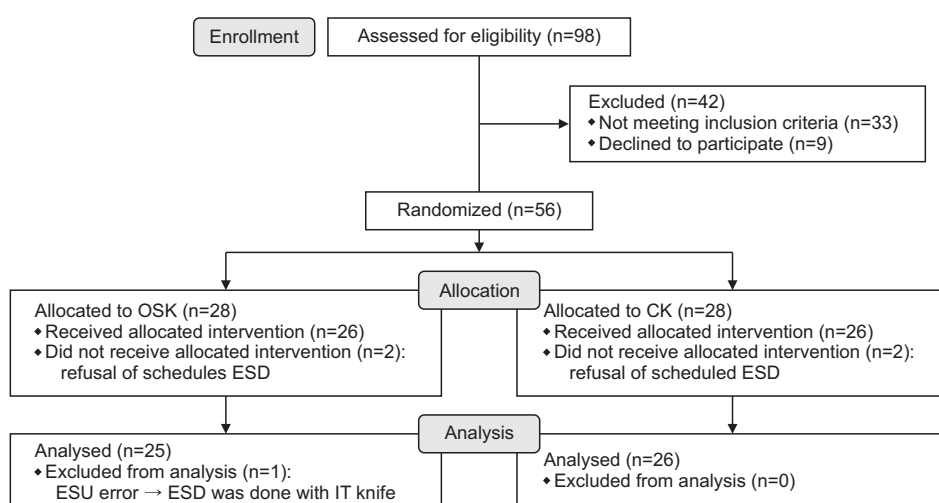There were no perforations during the ESD procedures; however, on second-look esophagogastroduodenoscopy,

Fig. 3. Flow diagram of this study. OSK, one-step knife; CK, conventional knife; ESD, endoscopic submucosal dissection; ESU, endoscopic surgical generating unit; IT, insulation-tipped.

Table 1. Demographic and Procedure Related Data

Variable	OSK (n=25)	CK (n=26)	p-value
Age, yr	60.0±9.1	68.0±8.8	0.117
Male sex	23 (92.0)	16 (61.5)	0.010
Chronic diseases			
HTN	12 (48.0)	11 (42.3)	0.683
Diabetes	7 (28.0)	6 (23.1)	0.687
Cardiologic disease	2 (8.0)	3 (11.5)	>0.999
CVA	0	0	NS
Site (body)	13 (52.0)	12 (46.2)	0.676
Sedation	25 (100)	26 (100)	NS
Sedatives[†]			
Midazolam	19 (76.0)	20 (76.9)	0.938
Propofol	14 (56.0)	15 (57.7)	0.903
Pethidine	17 (68.0)	20 (76.9)	0.475
Morphology[‡]			
Isp	2 (8.0)	2 (7.7)	>0.999
Is	1 (4.0)	0	0.490*
IIa	13 (52.0)	14 (53.8)	0.895
IIb	6 (24.0)	7 (26.9)	0.811
IIc	8 (32.0)	9 (34.6)	0.843
En bloc resected	25 (100)	26 (100)	NS
Previous diagnosis			0.090*
LGD	17 (68.0)	19 (73.1)	
HGD	4 (16.0)	3 (11.5)	
EGC	4 (16.0)	4 (15.4)	
Final diagnosis			0.331
LGD	16 (64.0)	11 (42.3)	
HGD	3 (12.0)	7 (26.9)	
EGC	6 (24.0)	8 (30.8)	
EGCs[‖]			
Lauren (intestinal)	5 (83)	7 (86)	>0.999
Location (upper)	2 (33)	3 (38)	>0.999
Submucosal invasion	0	1 (13)	NS
Mean diameter, mm	9.1±2.0	16.3±4.1	0.002

Data are presented as mean±SD or number (%).
OSK, one-step knife; CK, conventional knife; HTN, hypertension; CVA, cerebrovascular accident; LGD, low-grade dysplasia; HGD, high-grade dysplasia; EGC, early gastric cancer; NS, no significance.
*Statistically significant, p<0.05; [†]Concomitant use; [‡]Separately described overlapping lesions (e.g., IIa + IIc); [‖]EGCs are OSK (n=6) and CK (n=8).

Table 2. Injection Details and Maximum Diameter in Both Groups

Variable	OSK (n=25)	CK (n=26)	p-value*
Mean injection time, sec	39.0 (26.5–59.5)	87.5 (75.0–99.3)	<0.001
Total procedure time, min	18.0 (16.5–29.5)	28.1 (18.0–39.6)	0.055
Injection number, n	3.0 (2.0–6.5)	3.5 (3.0–5.3)	0.723
Total injection amount, mL	41.0 (20.0–54.0)	47.5 (36.8–78.3)	0.029
Amount per injection, mL	10.0 (6.5–13.0)	12.5 (10.0–18.5)	0.007
Maximal diameter, mm	26.0 (24.5–38.5)	31.0 (25.0–41.3)	0.280

Data are presented as median (interquartile range).
OSK, one-step knife; CK, conventional knife.
*Statistically significant, p<0.05.

we identified two cases of delayed bleeding in the OSK group, but they were easily controlled by endoscopic hemostasis.

DISCUSSION

Submucosal injection is an essential process that generates a submucosal cushion to prevent perforation during incision and creates the submucosal dissection area.[13,14]
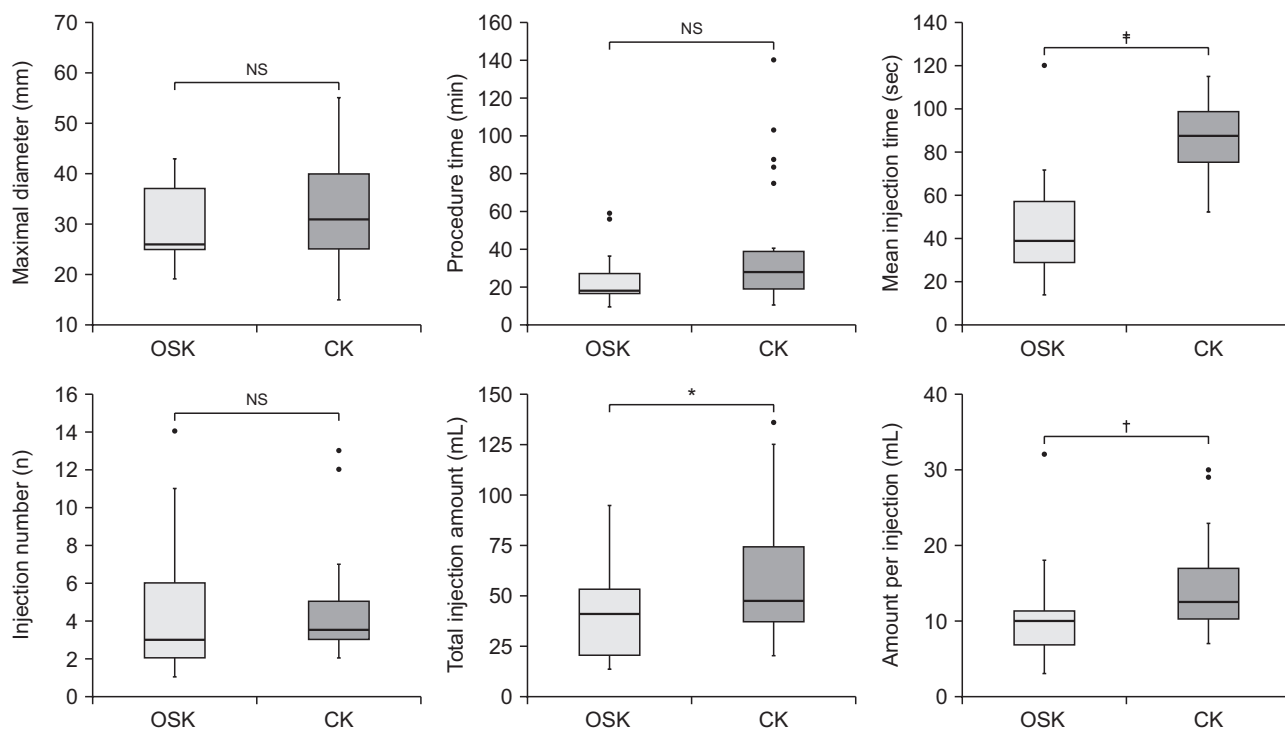
Fig. 4. Mann-Whitney U test box plots of mean injection time, total injection time, injection amount, injection number, and maximal diameter in both groups.
OSK, one-step knife; CK, conventional knife; NS, no significance. *p<0.05, †p<0.01, ‡p<0.001.

Table 3. Subgroup Analysis: Procedure Time According to Injection Number

Variable	Injection number 1–3			Injection number ≥4		
	OSK (n=13)	CK (n=13)	p-value*	OSK (n=12)	CK (n=13)	p-value*
Mean injection time, sec	55.0 (36.0–69.5)	88.0 (75.5–95.5)	0.006	31.0 (18.3–35.4)	84.0 (75.0–107.5)	<0.001
Total procedure time, min	17.0 (14.2–20.3)	22.3 (14.8–28.9)	0.293	26.7 (19.0–35.4)	35.0 (27.5–79.2)	0.044

Data are presented as median (interquartile range).
OSK, one-step knife; CK, conventional knife.
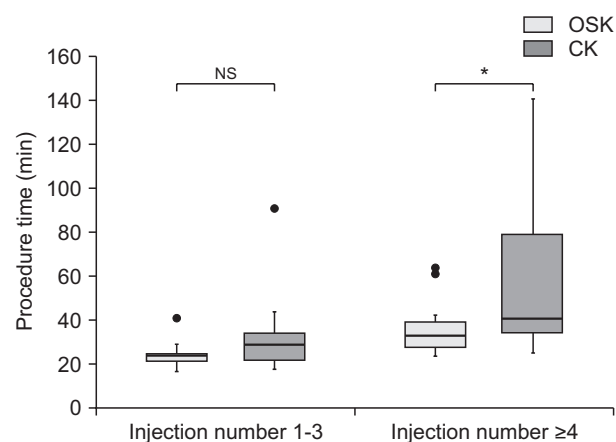*Statistically significant, p<0.05.

Fig. 5. Procedure time according to injection time.
OSK, one-step knife; CK, conventional knife; NS, no significance. *p<0.05.

Table 4. Results of Device Satisfaction Questionnaire

Very satisfactory	OSK (n=25)	CK (n=26)	p-value*
For endoscopists			
Overall	11 (44.0)	5 (19.2)	0.057
Procedure	7 (28.0)	2 (7.7)	0.075
Injection	10 (40.0)	2 (7.7)	0.009
For assistants			
Overall	18 (72.0)	13 (50.0)	0.108
Procedure	7 (28.0)	9 (34.6)	0.611
Injection	5 (20.0)	4 (15.4)	0.726

Data are presented as number (%).
OSK, one-step knife; CK, conventional knife.
*Statistically significant, p<0.05.

However, the time lag between submucosal injection and incision or dissection is inevitable. The conventional approach requires a time gap to wait and observe the disap-

pearance of the submucosal cushion. Several long-lasting solutions have been developed to overcome this time-consuming process; however, they are expensive compared with normal saline with epinephrine mixture.[15] In contrast, hybrid-type knives have been developed to have the dual-function of both a knife and injector, such as the Flush knife (Fujinon Optical Co.), Flush knife-BT (Fujinon Optical Co.), Splash M-knife (HOYA Corp.), and HybridKnife (Erbe Elektromedizin GmbH).[16-20] But these are not available in Korea.

It is established that the influencing factors on total procedure time are lesion size, lesion location, fibrosis, and endoscopist skill level.[10,21,22] We considered these influencing factors in our trial design and controlled for the bias of the lesions by including only 2 to 3 cm lesions without fibrosis, lesion location via implementing an upper to lower stratification, and endoscopist skill level by including those who have experience in performing ESD on more than 500 cases.

Our results demonstrated that the OSK markedly reduced the injection time from 87 to 39 seconds and displayed a trend to reduce the total procedure time from 28 to 18 minutes. It seems that the one of reason for 10-minute reduction in OSK group was that the lesions in standard knife groups were relatively larger. However, we think that the procedure was a little faster because the interval between using the knife after injection was short, so the procedure could be performed in a state where the submucosal fluid elevation was better maintained.

After additional analysis, there was a significant difference in the total procedure time (p=0.044) in ESD procedures requiring more than four injections compared with the difference in the total procedure time (p=0.293) in ESD procedures requiring less than three injections. This indicated that the OSK reduced the injection time and the total procedure time in cases required more submucosal injection.

In addition, lesions that require more frequent injections would indicate that they are more difficult. When we compared the injection frequency, the upper site received injections more frequently than the lower site (5.5±3.2 vs 3.5±2.6, respectively, p=0.016) (data not shown). Therefore, the OSK may be more helpful in facilitating difficult ESD procedures rather than simple ESD procedures.

The adverse events were only two cases of delayed bleeding in OSK group. They were easily controlled with hemostatic clips and coagrasper. One case in the OSK group was changed from OSK to IT knife 2, where OSK function did not work and the IT knife 2 did not work either. Later, the fault was known due to ESU.

The injection amount was significantly lower in the OSK group than in the CK group. We suspect that a smaller amount was administered in the OSK group because enough cushion remained at the time of knife use since there was no time lag. But we speculate that it did not make difference of injection time because the difference of injection amount was only 2 mL per injection.

Compared to endoscopists who expressed a satisfactory trend with the OSK, assistants did not express a satisfactory response. We consider that endoscopists did not find much difference between the OSK and CK procedures. In contrast, for assistants, the OSK procedure could be unfamiliar because it requires maneuvering the hand switch to switchover the device.

Initially, we calculated the sample size under the hypothesis that the OSK can reduce the injection time. However, we did not consider the total procedure time as a variable to calculate the sample size. Our results showed a significant difference in the injection time but not the total procedure time. We suspect that including more patients could result in a significant difference in the total procedure time. Moreover, we did not include lesions more than 3 cm in size or difficult lesions (with ulcers or fibrosis) which made an insignificant difference in point of total procedure time. Further study including cases with larger sized EGCs maybe needed. In Korea, most of submucosal injection solutions are normal saline with epinephrine mixture. So, we did not compare normal saline with epinephrine mixture with hyaluronic acid solution as submucosal injection solution in OSK. In addition, hybrid knifes such as dual knife J (Olympus) are not widely used in Korea. Therefore, we compared OSK with dual knife. Hybrid knife has a multiple function such as knife and injection. To validate the efficacy of the OSK approach for difficult ESD cases, a clinical trial with more diverse lesions and compared with hybrid knife for more large population would be needed.

In conclusion the OSK approach markedly reduced the submucosal injection time from 87 to 39 seconds and resulted in a trend that reduced the total procedure time from 28 to 18 minutes. In more difficult ESD cases that require more than four submucosal injections, the OSK may be a good choice for reducing the total procedure time.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: H.J.P. Data acquisition: H.K., H.S.K., S.Y.K., S.C.P., G.H.B., S.J.L. Data analysis and interpretation: H.K., J.W.K. Drafting of the manuscript; critical revision of the manuscript for important intellectual content: H.J.P., H.K., J.W.K. Statistical analysis: T.H.G. Obtained funding: H.J.P. Administrative, technical, or material support; study supervision: H.J.P. Approval of final manuscript: all authors.

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