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Cost-effectiveness and short-term clinical outcomes of argon plasma coagulation compared with endoscopic submucosal dissection in the treatment of gastric low-grade dysplasia

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Abstract

Endoscopic treatment such as endoscopic submucosal dissection (ESD) or argon plasma coagulation (APC) is widely performed to treat gastric low-grade dysplasia (LGD). We aimed to evaluate the clinical efficacy of APC versus ESD for gastric LGD in terms of cost-effectiveness. This was a retrospective review of patients with gastric LGD who were treated with endoscopic intervention (APC or ESD) between March 2011 to December 2015. Fifty-nine patients treated with APC and 124 patients treated with ESD were included. Patients in the APC group were significantly older (mean age, 67.68 vs 63.90 years, respectively, $P < .01$), had an increased rate of *Helicobacter pylori* infection (27.1 vs 10.5%, respectively, $P < .01$), and had a higher mean Charlson Comorbidity Index score (2.32 vs 0.38, respectively, $P < .01$) than those in the ESD group. The 2 groups did not differ in tumor size, location, macroscopic morphology, or surface configuration. The procedure time (11.31 vs56.44 minutes, respectively, $P < .01$), and hospital stay (3.2 vs 5.6 days, respectively, $P < .01$) were significantly, shorter in the APC group than in the ESD group. Additionally, the cost incurred was significantly, lower in the APC group than in the ESD group (962.03 vs 2,534.80 dollars, respectively, $P < .01$). APC has many advantages related to safety, and cost-effectiveness compared with ESD. Therefore, APC can be considered an alternative treatment option for gastric LGD.

Abbreviations: APC = argon plasma coagulation, ESD = endoscopic submucosal dissection, HGD = high-grade dysplasia, LGD = low-grade dysplasia.

Keywords: argon plasma coagulation, cost-effectiveness, endoscopic submucosal dissection, low-grade dysplasia

1. Introduction

Gastric cancer remains one of the most common cancer, although its proportion among the major cancers was decreasing from top in the year 1975 to the fifth place in the year 2012.[1,2] Each year about 1 million gastric cancer cases are diagnosed, and this number is likely to increase as populations age worldwide. Gastric adenoma is a precursor to gastric cancer. As upper endoscopy has been widely, performed in stomach cancer screening, diagnosis of both gastric adenomas and gastric cancers has been increasingly improved. Some studies,[3] report that 97% of gastric low-grade dysplasia (LGD) shows no histological changes, and 95% shows no increases in size. Even 11% has a reduction in size. Furthermore, there was 11% reduction in size. Therefore, gastric LGD has benign natural course.

However, few definite guidelines regarding the management of LGD are available. Given the lower-risk of malignant transformation, some investigators recommend annual endoscopic surveillance with rebiopsy for LGD,[4,5] whereas others suggest active resection. Endoscopic resection is less invasive than surgical resection but also has a risk of complications, and requires high endoscopic skill. In the revised Vienna classification, endoscopic treatment or follow-up is recommended for LGD.[6]

Endoscopic treatment for gastric epithelial tumor is widely performed because of its technical and instrumental improvements. Endoscopic submucosal dissection (ESD) allows en bloc resection of early gastric carcinomas, and gastric adenomas,[7] thereby enabling an accurate histological diagnosis. However, ESD may lead to a significant increase in the cost of care, and risk of complications such as bleeding, and perforation.[8] Moreover, it is a serious issue in elderly and high-risk patients.

Argon plasma coagulation (APC) is a method of contact-free electrocoagulation that transfers a high-frequency electric current through ionized argon gas to the lesion.[9] APC is less invasive; thus, it has been used to treat patients with gastric adenoma, or early gastric cancer (EGC) with intramucosal invasion, who cannot undergo endoscopic resection, or open surgery.[10] APC can also be performed by a less experienced gastrointestinal endoscopist, and does not require the skill level needed for

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endoscopic resection. However, APC is used in a limited number of patients due to difficulty in predicting invasion depth, and an inability to perform pathologic evaluations.[10–12] ESD is considered the best treatment for gastric high-grade dysplasia (HGD). However, considering the less progressive nature of gastric LGD, risk of complications, and cost of endoscopic resection, APC may provide another treatment option for LGD. However, little is known about the comparative results of APC versus ESD for gastric LGD. Therefore, here we aimed to evaluate the clinical efficacy, and cost-effectiveness of APC compared with that of ESD for gastric LGD.

2. Materials and methods

2.1. Study population

This was a retrospective review of patients with gastric LGD who were treated with endoscopic intervention between March 2011 to December 2015 at Chung-Ang University Hospital, Seoul, Korea. Gastric LGD was confirmed by forceps biopsy, and esophagogastroduodenoscopy (EGD; GIF-H260 or GIF-Q260; Olympus, Tokyo, Japan). During the EGD, if dysplasia or carcinoma was suspected, between 2 to 4 biopsy samples were obtained using forceps (FB-25 K-1; Olympus, Tokyo, Japan, or BX 420; PriMed Instruments Inc., Ontario, Canada). We limited the size of LGD to 2.0 cm. Baseline characteristics including sex, age, Charlson comorbidity score, *Helicobacter pylori* (*H. pylori*) infection status, follow-up duration, and medication history of the patients were investigated. This study protocol was approved by the Institutional Review Board of the Chung-Ang University Hospital, Korea (IRB No. C2015212 (1670), which waived the need for written informed consent.

2.2. Evaluation of endoscopic features

Lesion size, location, gross appearance, and surface configuration were investigated. Lesion size was measured macroscopically with an endoscopic ruler, and microscopically via thorough pathologic examination. APC and ESD for LGD ≥ 2.0 cm were excluded. Lesion locations were classified into the upper, middle, and lower third of the stomach with the following anatomical considerations: upper third contains the fundus, cardia, and upper body; middle third contains the mid body, and lower body; and lower third contains the angle and antrum.

The Paris classification,[13] which classifies lesions as elevated, flat, or depressed, was used to define the gross appearance of the superficial lesions. Surface configuration (including the presence of erythema, nodularity, erosion, and ulceration) was also examined. Erythema was defined as reddish coloration of the mucosal surface of the lesion compared with the surrounding mucosa. Nodularity was defined as the presence of an irregularly nodular or raised mucosa. Lesions combined with ulcerations, or scarring from a previous ulceration (converging folds or fibrosis in the submucosa) were considered ulcerations.

2.3. Endoscopic procedures

Patients were free to choose the treatment option, APC or ESD, after hearing a full standardized explanation from the doctors. All lesions were removed by ESD or APC by 2 experienced gastrointestinal endoscopists (B.J.K., and J.G.K.) using a single-channel endoscope (GIF-Q260J, GIF-H260Z or GIF-H290; Olympus, Tokyo, Japan). Patients were sedated using a course of intravenous midazolam (0.05 mg/kg) with pethidine (50 mg) as needed. Chromoendoscopy was routinely, performed to identify tumor shape, and margin by spraying it with indigo carmine (0.1–0.5%).

The equipment for APC included a high-frequency electrosurgical current generator (VIO 300D; ErbeElektromedizin, Tübingen, Germany). The argon gas flow rate was 2.0 L/minutes, with the current set at 40W and in the pulsed mode. APC was performed using a straight-type probe. After spraying indigo carmine solution onto the lesion, the area around the tumor was marked with APC. Normal saline solution was injected into the submucosal layer under the lesion with a standard disposable 23-G injection needle. A saline solution (100 ccs of 0.9% saline mixed with 1 mg of epinephrine and a small amount of indigo carmine) was injected into the submucosal layer for better identification of the tissue layer. Normal saline was injected until a desirable amount of submucosal swelling was achieved. The region inside the designated area was evenly, treated with APC until the lesion had completely coagulated, and appeared dry on endoscopic examination.

For ESD, first, markings using dots were made 2 mm beyond the tumor margins with APC. A Cerol solution (containing fructose, concentrated glycerin, and sodium chloride) was then injected into the submucosal layer around the lesion, and the submucosal layer was dissected using a needle knife (Nadel-Papillotom; 99020121, MTW endoskopie, Wesel, Germany), insulated-tip knife (KD-611L; Olympus, Tokyo, Japan), and/or flex knife (KD-630L; Olympus, Tokyo, Japan). If required during the procedure, the saline injection was repeated to achieve endoscopic hemostasis. A high-frequency electrosurgical current generator (VIO 300D; ErbeElektromedizin, Tübingen, Germany) was used during marking, mucosal incision, subtumoral dissection, and hemostasis. Complete resection was defined as a resected tumor with tumor-free lateral and deep margins.

2.4. Management after APC or ESD

After APC or ESD treatment, patients were closely, observed. If there were no specific complaints during the hospital stay, patients were discharged with proton pump inhibitors as scheduled.

In cases of APC, all patients received 40 mg of pantoprazole intravenously, or took 30 mg of lansoprazole orally once daily on the day they underwent APC, and maintained the dosage for 2 to 4 weeks. If no APC related complications occurred, a soft diet was allowed on the first day after APC, and the patients were discharged the day they began the diet, which was usually, the second day after APC.

In cases of ESD, all patients received 40 mg of pantoprazole intravenously, or took 30 mg of lansoprazole orally once daily on the day they underwent ESD, and throughout the length of their hospital stay, which was usually between 3 to 4 days. If no ESD related complications occurred, a liquid diet was started on the second day after ESD. The patients were discharged the second day after beginning the diet. After discharge, patients were instructed to take 30 mg of lansoprazole once a day for 4 weeks.

EGD with a biopsy was scheduled for 3 months after the APC, or ESD to observe healing of the artificial ulcer, and detect the presence of any residual lesions. After the initial evaluation, EGD was performed every 12 months to detect recurrence. A residual tumor was defined as a gastric adenoma found on forceps biopsy in a previously, treated site at 3 months after the first treatment.

Regarding the complications, bleeding was classified as massive or delayed bleeding. Massive bleeding was defined as a decrease in blood hemoglobin level of ≥ 2 g/dL that was accompanied by the occurrence of hematemesis, melena, or the combination of unstable vital signs, and fresh blood, or clots upon Levin tube irrigation within 4 weeks after the endoscopic treatment. Delayed bleeding was defined as post-procedural bleeding requiring additional endoscopic management, and a post-procedure lesion belonging to Forrest classification Ia, Ib, or IIa. Perforation was classified as macroperforation, or microperforation.[14] Macroperforation was a perforation readily recognized endoscopically, whereas microperforation was a perforation detected by the presence of free air on plain radiographs taken after the procedure.

2.5. Statistical analysis

Categorical variables were evaluated using the χ^2 test or Fisher's exact test. Continuous variables were evaluated using Student's t-test. Continuous variables are shown as mean ± standard deviation. P values < .05 were considered statistically, significant. The software package used for analysis was SPSS version 12.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

A total of 183 patients were included in this study: 59 patients in the APC group, and 124 in the ESD group (Fig. 1). Table 1 shows the patients' baseline characteristics. The 2 groups did not differ significantly, in sex, use of hazardous drugs, or follow-up duration. Hazardous drugs were defined as aspirin, nonsteroidal anti-inflammatory drugs, anti-platelet drugs, anti-coagulant drugs, and steroids. However, patients in the APC group were significantly, older than those in the ESD group. The mean ages between the APC and ESD groups were 67.68 to 63.90 years, respectively ($P < .01$). The mean Charlson Comorbidity Index score was higher in the APC group than in the ESD group (2.32 vs 0.38, respectively, $P < .01$). The *H. pylori* infection rate was higher in the APC group than in the ESD group (27.1 vs 10.5%, respectively, $P < 0.01$).

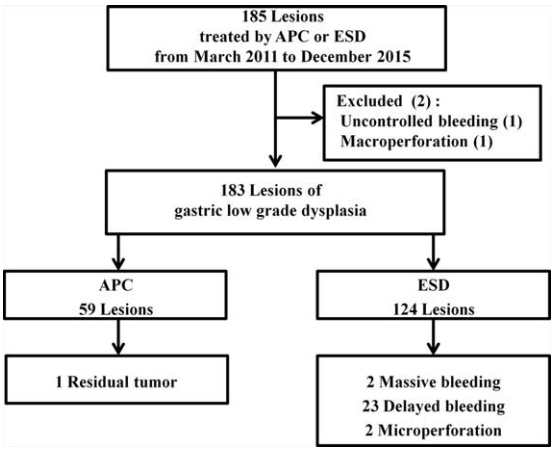

Figure 1. Clinical outcomes between APC and ESD. Among 183 gastric low-grade dysplasia lesions, 59 were treated with APC and 124 were treated with ESD. After endoscopic treatment, 1 residual tumor was found in the APC group, whereas 2 cases of massive bleeding, 23 of delayed bleeding, and 2 of microperforation occurred in the ESD group. APC = argon plasma coagulation, ESD = endoscopic submucosal dissection.

Table 1

Patient characteristics of gastric LGD.

	APC group n = 59	ESD group n = 124	*P* value
Age, mean ± SD (years)	67.68 ± 8.32	63.90 ± 9.38	<.01
Sex, n (%)			.83
Male	39 (66.1%)	80 (64.5%)	
Female	20 (33.9%)	44 (35.5%)	
Charlson score, mean ± SD	2.32 ± 1.18	0.38 ± 0.66	<.01
H.pylori infection, n (%)			<.01
Infected	16 (27.1%)	13 (10.5%)	
Not infected or unknown	43 (72.9%)	111 (89.5%)	
Hazard drug*, n (%)			.93
Use	13 (22.0%)	28 (22.6%)	
Not use	46 (78.0%)	96 (77.4%)	
Follow-up duration (month)	21.27 ± 15.06	21.87 ± 17.12	.82

APC = argon plasma coagulation, ESD = endoscopic submucosal dissection, LGD = low-grade dysplasia, SD = standard deviation.
* Aspirin, NASIDs, anti-platelet, anti-coagulant, steroid.

3.2. Tumor characteristics

Tumor characteristics between the APC and ESD groups are summarized in Table 2. Among the patients, 4 had 2 lesions, including 1 in the APC group, and 3 in the ESD group. The 2 groups did not differ significantly, in tumor size, location, macroscopic morphology, or surface configuration.

3.3. Comparison of outcomes between the APC and ESD groups

Clinical outcomes between the APC and ESD groups are summarized in Table 3. We compared procedure time and hospital stay between the 2 groups. The mean procedure time was significantly shorter in the APC group than in the ESD group (11.31 ± 8.23 vs 56.44 ± 35.28 minutes, respectively, $P < .01$). The mean hospital stay was significantly shorter in the APC group than in the ESD group (3.2 ± 0.8 vs 5.6 ± 1.4 days, respectively, $P < .01$). In particular, we compared total cost between the 2 groups. The cost was significantly lower in the APC group than in the ESD group (962.03 ± 204.40 vs 2,534.80 ± 648.11 dollars, respectively, $P < .01$).

There was a significant difference in complication rate between the 2 groups. There was only 1 (1.7%) complication in the APC

Table 2

Tumor characteristics of gastric LGD.

	APC group n = 59	ESD group n = 124	*P* value
Size, mean ± SD (mm)	11.36 ± 3.45	11.14 ± 5.23	.74
Location, n (%)			.42
Upper third	6 (10.2%)	7 (5.6%)	
Middle third	9 (15.3%)	15 (12.1%)	
Lower third	44 (74.6%)	102 (82.3%)	
Macroscopic morphology, n (%)			.77
Elevated	50 (83.6%)	103 (83.1%)	
Flat or depressed	9 (16.4%)	21 (16.9%)	
Surface configuration, n (%)			.27
Erythema	2 (3.4%)	7 (5.6%)	
Nodularity	52 (88.1%)	94 (75.8%)	
Erosion	4 (6.8%)	20 (16.1%)	
Ulcer	1 (1.7%)	3 (2.4%)	

APC = argon plasma coagulation, ESD = endoscopic submucosal dissection, LGD = low-grade dysplasia, SD = standard deviation.

Table 3

Outcomes of endoscopic treatment between the APC and ESD groups.

	APC group n = 59	ESD group n = 124	*P* value
Procedure time, mean ± SD (min)	11.31 ± 8.23	56.44 ± 35.28	<.01
Admission days, mean ± SD (days)	3.2 ± 0.8	5.6 ± 1.4	<.01
Total cost, mean ± SD (dollars)	962.03 ± 204.40	2,534.80 ± 648.11	<.01
Procedure-related cost	135.11 ± 25.02	552.68 ± 208.64	.027
Equipment and accessory	95.50 ± 1.06	338.10 ± 78.75	<.01
Complication, n (%)	1 (1.7%)	27 (21.8%)	<.01
Massive bleeding	0	2 (1.6%)	
Delayed bleeding	1 (1.7%)	23 (20.2%)	
Macroperforation	0	0	
Microperforation	0	2 (1.6%)	
Residual tumor, n (%)	1 (1.7%)	0	.15

APC = argon plasma coagulation, ESD = endoscopic submucosal dissection, SD = standard deviation.

group whereas 27 patients (21.8%) experienced a complication in the ESD group. The most common complication in the APC group was delayed bleeding. Massive bleeding occurred in 2 patients and delayed bleeding occurred in 23 patients in the ESD group. All patients with complications were successfully, managed using an endoscopic hemostatic technique (hemoclip or electric coagulation), and recovered completely. No patient required surgery or angiographic intervention. Microperforation occurred in 2 patients in the ESD group, and each recovered completely, after conservative management.

3.4. Clinical outcomes of patients with residual tumor

A residual tumor was evident in 1 patient after APC treatment. The residual tumor was treated by APC again, and no recurrence occurred during the follow-up period. There were cases of residual tumor in the ESD group.

4. Discussion

The present study demonstrated the clinical efficacy, and cost-effectiveness of APC versus ESD for the treatment of LGD. Our data show that APC was a more cost-effective treatment modality than ESD; the benefit of the former in terms of cost-effectiveness included a shorter procedure time, and duration of hospital stay with a lower complication rate compared to the latter. Although technical, and instrumental improvements have extended the indications for these elegant techniques in patients with gastric neoplasm,[15] endoscopic resection remains technically difficult, and cannot be performed in some cases because of the high-risk of bleeding, or perforation, or non-lifting after the submucosal saline injection.

APC has been used to treat a broad range of gastrointestinal conditions, including bleeding ulcers,[16] Dieulafoy's lesions,[17] hemorrhagic telangiectasia,[18] varices,[19,20] and tumors.[10] Recent studies have shown that APC is an effective, and safe treatment option for neoplasms of the gastrointestinal tract.[10,12,21,22] Thus, APC can be considered a reasonable treatment option for gastric adenomas with LGD as it is less invasive for patients at high risk of surgical complications or for those who refuse surgery. However, the efficacy and cost-effectiveness of APC in gastric LGD have not been elucidated.

A few studies have shown that APC is an effective and safe treatment option for early gastric neoplasm.[22–25] APC is also useful for the follow-up treatment of EGC after endoscopic mucosal resection.[11] However, no study has compared the efficacy and cost-effectiveness of APC to that of ESD. Our study showed that APC was significantly, superior to ESD with respect to cost, procedure time, and hospital stay. The mean total cost between APC and ESD was 962 and 2535 dollars, respectively. The mean procedure time for the APC, and ESD groups was 11, and 56 minutes, respectively. The mean hospital stay in the APC, and ESD groups was 3.2, and 5.6 days, respectively. These data indicate that APC is more economical than ESD. Moreover, Tomita et al[22] reported that endoscopic experience did not influence APC outcomes (including recurrence rate and adverse events). Therefore, APC might be operator-independent, and non-experienced endoscopists may treat small gastric LGD lesions without a long training period such as that required for ESD.

Some studies have shown that although many cases of gastric LGD regress, or persist, some reportedly, progressed to HGD, or carcinoma after a median follow-up period ranging between 34.5 to 41.5 months.[26,27] This long time interval indicates that gastric adenoma with LGD rarely contains carcinoma at the time of diagnosis and has a less progressive nature. No therapeutic guidelines are established for gastric LGD because of these characteristics. Some researchers consider annual endoscopic surveillance with rebiopsy appropriate.[4,5] However, problems with this approach include the risk of disease progression, patient anxiety, and low compliance with frequent, and costly, follow-up studies for an undefined period.[9,28] The present study showed only 1 case of residual tumor in the APC group. The residual tumor rate was only 1.7% in the APC group. Therefore, regarding the benign course of LGD, APC in gastric LGD is a relatively, effective, and safe treatment tool.

For endoscopic treatment, histological assessment is crucial for determining whether the lesions were treated successfully, or additional surgery is needed. However, histology cannot be evaluated in APC because the coagulation that occurs from the treatment causes necrosis of the tumorous tissue. This is 1 reason why APC alone has not been used as a first-line therapy for EGC or HGD until now. However, relatively, considering the benign course of gastric LGD, its treatment should differ between EGC or HGD. Although endoscopic resection is less invasive than surgical resection, it can carry the risk of complications such as bleeding and perforation. In our study, there were no cases of perforation, and massive bleeding, and only 1 case of delayed bleeding in the APC group, compared with 2 cases of massive bleeding, 2 cases of perforation, and 23 cases of delayed bleeding in the ESD group. ESD might be an excessive and relatively, risky procedure for the treatment of all gastric LGD lesions.

It has recently, been suggested that *H. pylori* infection can be a risk factor for gastric adenoma.[29] The infection induces an

irreversible mucosal change and provides an environment for the gastric tumor to recur at multiple sites. Patients with *H. pylori* infection have an increased risk of metachronous lesion, and meticulous endoscopic follow-up is important after the treatment of gastric adenoma. This study shows that patients treated with APC had higher rates of *H. pylori* infection. In addition, patients in the APC group were significantly, older, and had higher Charlson Comorbidity Index scores than those in the ESD group. The 2 groups did not differ in terms of tumor size, location, macroscopic morphology, and surface configuration. This indicates that, given the same tumor characteristics, the APC group was at higher risk in surgery. However, this study showed that APC was more cost-effective and less harmful than ESD.

In this study, all tumor lesions were ≤ 2 cm. In general, larger size, and flat, or depressed tumors can be underestimated endoscopically.[30] Thus, some flat tumors that are ≥ 2 cm should be dissected via ESD.

This study has several limitations. Firstly, it was a single-center study with a limited number of patients. Secondly, selection bias likely played a role in the choice of treatment modality. Thus, randomized prospective studies are necessary to establish clinical applications and the most effective treatment modality for gastric LGD. Lastly, we evaluated short-term effects, so long-term follow-up evaluations are needed to establish treatment options.

In conclusion, APC has many safety, and cost-effectiveness advantages, including short operation time, low medical cost, shortened hospital stays, procedural ease, favorable outcomes, and lack of serious complications irrespective of the selected endoscopic option compared with ESD. Therefore, APC should be considered an alternative treatment option for patients with gastric LGD if proper follow-up checks are performed.

Author contributions

BJK conceived and designed the study. BJK and JGK collected the data. IKS analyzed the data. BK wrote the manuscript.
Conceptualization: Beom Jin Kim.
Data curation: Bomin Kim, Il-Kook Seo.
Investigation: Jae Gyu Kim.
Methodology: Bomin Kim.
Resources: Bomin Kim, Il-Kook Seo.
Supervision: Beom Jin Kim.
Writing – original draft: Bomin Kim.
Writing – review & editing: Beom Jin Kim.

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