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Original Article

Safety and long-term efficacy of hybrid-argon plasma coagulation for the treatment of Barrett's esophagus: An Australian pilot study (with video)

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A B S T R A C T

Background: Five to ten percent of all patients undergoing radiofrequency ablation (RFA), which is the most established technique for Barrett's esophagus (BE) ablation-develop strictures. Hybrid-argon plasma coagulation (APC) combines APC with submucosal saline injection that was recently developed to tackle this problem. The aims of this pilot study were to evaluate the feasibility, tolerance, safety and long-term efficacy of hybrid-APC for the treatment of BE.

Methods: Patients with histological proven BE were selected for hybrid-APC. Prior to APC thermal ablation the mucosa was lifted using a submucosal high-pressure water jet injection system (Erbejet 2; Erbe, Tuebingen, Germany). Short-term (< 48 hours) and long-term (> 48 hours) safety were evaluated. Efficacy of ablation was measured at 3, 6, 12 and 24 months at follow-up endoscopy by evidence of macroscopically complete resolution of BE mucosa and/or histologically complete resolution of intestinal metaplasia (CRIM).

Results: Eleven patients were included in the study (average age, 68.2 years; male 72.7%). Eight patients (72.7%) were treatment naive, 9.1% ($n = 1$) had prior RFA and 18.2% ($n = 2$) had prior endoscopic mucosal resection. Two patients were excluded from the study. Nine patients (100%) had macroscopic remission and 88.9% ($n = 8$) had macroscopic remission and microscopic CRIM at 24 months after hybrid-APC ablation. No treatment-related stricture or other major complications were observed, 1 patient (11.1%) reported minor adverse effects.

Conclusion: In this prospective pilot study, hybrid-APC appears safe, feasible and effective after 24 months, which has not been evaluated so far. Further large, multi-centre trials are warranted to confirm the present results.

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Keywords: Argon plasma coagulation; Barrett esophagus; Surgical endoscopy

Introduction

Barrett's esophagus (BE) occurs when the squamous epithelium that normally lines the distal esophagus is replaced with columnar epithelium. This transformation develops as a consequence of chronic gastroesophageal reflux disease and is associated with an increased risk of esophageal adenocarcinoma.^{1,2} The approach to a patient with BE depends on presence of and the level of dysplasia. Anti-reflux therapy and endoscopic surveillance is indicated for patients with BE.² If dysplasia or an early cancer stage is detected and confirmed by two experts in gastrointestinal pathology, endoscopic mucosal resection (EMR) or endoscopic submucosal dis-

section (ESD) of all visible lesions followed by ablation therapy of the non-neoplastic Barrett's mucosa is recommended.^{3–5} Several studies have reported remission rate up to 90% at 5-year follow-up when combining those two techniques.^{6–8}

Radiofrequency ablation (RFA) is the current modality accepted as standard of care for ablation of dysplasia.² However, RFA has some shortcomings and limitations. Firstly, upper gastrointestinal haemorrhage, chest pain and strictures have been reported as adverse events. The stricture rate post RFA is estimated at 6%.⁹ Secondly, recurrences of both BE and neoplasia are observed in up to 14% of patients.^{5,8,10} Last but not least, RFA devices are not commonly available and are costly.

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Argon-plasma coagulation (APC) is another ablation technique which has been used for the treatment of dysplastic BE.^{11–13} However, the procedure is associated with risks of perforation, stricture formation, and buried glands which may carry a risk of malignant transformation.¹⁴ In order to reduce those complications, particularly stricture formation, hybrid-argon plasma coagulation (hybrid-APC) was developed. This emerging method combines submucosal saline lift with diffuse tissue thermal ablation. Manner et al¹⁵ and Kashin et al¹⁶ demonstrated that hybrid-APC was safe with a stricture rate of 2% and effective. However, the follow-up period was in both studies only a few months. The aim of our study was to prospectively evaluate the safety and long-term efficacy of hybrid-APC for the treatment of dysplastic BE.

Methods

The study was carried out in a single tertiary hospital setting. All consecutive patients with biopsy proven BE with either low-grade dysplasia (LGD), high-grade dysplasia (HGD) or T1a adenocarcinoma, confirmed by two expert pathologists were included in the study (Table 1). Ethics approval was granted from the Sydney Local Health District Human Research Ethics Committee and the study was registered at the Australian and New Zealand trials registry (ACTRN12617000402347). Informed consent was obtained from all patients to be included in the study.

The length of the BE was measured endoscopically and classified into a short-segment Barrett's esophagus (SSBE) or long-segment Barrett's esophagus (LSBE) according to the Prague criteria.¹⁷ The BE was inspected with high definition white light, narrow band imaging and acetic acid spray. Macroscopically suspicious neoplasia areas were resected endoscopically with EMR technique prior to the ablation (captivator EMR kit; Boston Scientific, Natick, MA, USA) in order to distinguish between histological T1a and $\geq$ T1b. One endoscopist (PS) performed the ablation using a standardized technique as follows: a transparent cap was attached to the tip of the endoscope. The hybrid-APC probe (axial, outer diameter [distal] 2.3 mm, length 2.2 m; Erbe, Tuebingen, Germany) was introduced into the esophagus through the working channel and under real time visualization. Subsequent injection

of a 0.9% sodium chloride solution into the submucosa of the Barrett's mucosa was performed with the hybrid-APC probe and the high-pressure needleless water jet system (ErbeJet 2; Erbe) that creates a safety cushion under the mucosa (Fig. 1, Supplementary Video 1). After injection, the area was ablated with the hybrid-APC probe (Pulsed APC, effect 2, 60–70 Watts) (Fig. 2, Supplementary Video 1). Only hemi-circumferential hybrid-APC was performed in each setting. All procedures were carried out with monitored anaesthesia (propofol sedation).

Hybrid-APC therapy was performed at 12 weekly intervals until complete remission of BE (CRIM) was achieved (both endoscopically and histologically). At surveillance endoscopies, four-quadrant biopsies in the area of the former BE segment starting at the neo-Z-line and at intervals of 2 cm were obtained. Patients underwent endoscopic follow-up at 3, 6, 9, 12, 18, 24, 30, and 36 months with biopsies taken at each endoscopy as described above (Fig. 3).

All patients were prescribed high dose proton pump inhibitor

Fig. 1. Sodium chloride solution (0.9%) injection and submucosal lifting.

Fig. 2. Hybrid-argon plasma coagulation treatment of the Barrett's esophagus.

Table 1 Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Patients 18–85 years of age	Adenocarcinoma with histological diagnosis of $\geq$ T1b
Informed consent	Pregnancy
Patients with a Barrett's esophagus with a baseline confirmed histological diagnosis of low-grade dysplasia, high-grade dysplasia or T1a adenocarcinoma	Significant oesophageal stenosis prior to initial hybrid-APC treatment defined as a stenosis that cannot be passed by a therapeutic endoscope or a stenosis
	Patients with incomplete healing post-endoscopic resection despite adequate PPI-medication
	Presence of esophageal varices
	Anticoagulant therapy that cannot be discontinued prior to hybrid-APC or incorrectable hemostatic disorders
	Life expectancy less than 2 years

APC, argon plasma coagulation; PPI, proton pump inhibitor.

Fig. 3. Oesophagus after hybrid-argon plasma coagulation treatment.

treatment (Pantoprazole 40 mg twice daily) for the entire duration of endoscopic therapy. After they achieved remission, they were placed on pantoprazole 40 mg daily. Patients were commenced on a liquid diet immediately post procedure followed by a soft diet for 3 days. Thereafter, normal diet was resumed. Patients were offered sucralfate, 1 g (four times daily) for 3 days post procedure if they experienced pain or dysphagia post procedure. All patients were followed up clinically, 7 days post procedure.

Data were analysed descriptively. Baseline characteristics of the patient population, BE characteristics, technical details, and procedure outcomes were summarized as means (standard deviation) or medians (with interquartile range and range) for continuous data, and as frequencies and proportions for categorical data. All statistical analysis was performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA). All authors had access to the study data and reviewed and approved the final manuscript.

Results

From April 2017 to April 2018, 11 patients (72.7% male; mean age, 68.2 ± 8.0 years) were included in the study (Table 2). Five patients had LGD, 4 patients had HGD and 2 patients had T1a adenocarcinoma. Two patients (18.2%) underwent EMR prior to ablation, one patient (9.1%) had prior RFA. Only patients with greater than 24-month follow-up were included in the analysis. As such, two patients (18.2%) were excluded from the analysis. One patient with human immunodeficiency virus (HIV) and spinal injury declined to continue follow-up; however, he remained in remission at 12-month post ablation (3 hybrid-APC sessions for HGD). The second patient was lost to follow-up at 6 months after 3 hybrid-APC ablations for LGD. Both patients did not report any adverse events and remained in remission when they stopped follow-up.

The mean duration of hybrid-APC treatment was 3.5 minutes (± 1.4 minutes).

In total, mean 2.7 sessions (± 1.1 sessions) were required to achieve CRIM. At 6, 12, and 24 months, the percentage of macroscopic complete remission of BE was 100%. Histologic CRIM was achieved in all patients at 6, 12, and 18 months. However, at 24 months, one patient (11.1%) had histologic evidence of relapse (LGD). The mean follow-up was 28.8 months (± 4.4 months).

Table 2 Patient's Characteristics

Variable	Value
Age (yr)	68.2 ± 8.0
Sex distribution	
Male	8 (72.7)
Female	3 (27.3)
Grade	
LGD	5 (45.4)
HGD	4 (36.4)
T1a	2 (18.2)
Type of BE	
SSBE	7 (63.7)
LSBE	4 (36.3)
Prague classification (cm)	
C value	3.1 ± 2.5
M value	4.5 ± 4.0

Values are presented as number (%) or mean $\pm$ standard deviation.

LGD, low-grade dysplasia; HGD, high-grade dysplasia; SSBE, short-segment Barrett's esophagus; LSBE, long-segment Barrett's esophagus.

One patient (11.1%) had a minor adverse event with mild odynophagia lasting 3 days after the first hybrid-APC treatment. No short- or long-term serious adverse events were observed. In particular, no patient developed a stricture during treatment or the follow-up period.

Discussion

A multimodal approach using a combination of focal endoscopic resection for visible and suspicious lesions followed by ablation therapy for HGD as well as early cancer is currently gold standard treatment.^{2,5,18} Furthermore, ablation treatment of LGD is associated with reduced rates of progression to HGD or esophageal adenocarcinoma and is commonly performed.¹⁹ A variety of techniques are available to perform ablation, such as cryotherapy APC and hybrid-APC.^{5,20} Despite the emergence of several new modalities, RFA remains the most widely performed endoscopic ablation procedure for BE due to its ease of use and high degree of efficacy.² However, up to 14% of the patients undergoing RFA have recurrences of both BE and neoplasia within 2 years and strictures arise in about 6% of patients.^{5,8–10}

Our prospective study demonstrates that hybrid-APC has a favourable safety profile. Neither strictures nor other major side effects were observed. In two other recently published retrospective studies on the use of hybrid-APC, the stricture rate was 0% and 2%, respectively.^{15,16} A German group showed in a randomized ex-vivo study that prior submucosal saline injection appears to be able to reduce the coagulation depth by half in comparison with standard APC, with no thermal injury to the propria muscularis.²¹ This water cushion may explain the lower rate of stricture formation observed with this technique in comparison to traditional APC. A lower rate of stricture formation appears to be a major advantage of hybrid-APC compared with RFA; however, large multi-centre prospective trials are needed to determine this.

Our pilot study shows that hybrid-APC is not only safe, but also effective for BE ablation. Macroscopic remission was achieved in 100% of patients after 24 months. CRIM rate was 88.9% at long-term follow-up. Surprisingly, a patient was com-

pletely healed of BE after one year but developed recurrence after 24 months (LGD). This highlights the need for long-term data in this area and ongoing surveillance of patients with dysplastic Barrett's oesophagus.

There is a paucity of data on the efficacy of hybrid-APC. Although Kashin et al¹⁶ and Manner et al¹⁵ showed similar results, their mean follow-up after hybrid-APC was only 3 to 4.5 months. The CRIM rate of APC treatment without prior submucosal saline injection varies between 50% and 77%.^{22,23} Hybrid-APC appears to be more effective than conventional APC as a larger area of BE can be thoroughly ablated due to the prior submucosal saline injection.^{24,25} The five-year follow-up data from RFA suggests that eradication of the BE is maintained in roughly 85% to 90% of patients.^{7,26}

In comparison to RFA, hybrid-APC is possibly less suitable for extremely long BE, although the longest extent of BE in our study was 13 cm (Prague C13M13) and no complications were observed. Submucosal saline injection was feasible in all patients, even those with post EMR scarring.

Costs are an evident factor when selecting a therapeutic device. Although a full cost analysis was beyond the scope of this study, the cost of RFA catheters are substantially higher than hybrid-APC catheters. The material costs for a treatment with a hybrid-APC probe amount to approximately Australian dollar (AUD) 950.00 (hybrid-APC, AUD 840.00 + Pump Cartridge, AUD 105.00), whereas costs are approximately AUD 1,800 for the RFA HALO-90 catheter. In addition, although the initial procurement costs for the RFA generator are cheaper (18,000 AUD vs 46,000 AUD for the Erbejet 2 machine), Erbejet 2 is also used in liver resection surgery and as such is commonly available in major centres. Furthermore, unlike RFA, hybrid-APC does not require the use of an over-the-scope apparatus, which can be challenging to advance past the oropharynx and upper esophageal sphincter.

After hybrid-APC or any thermal ablation therapy, acid suppressive therapy is vital. It prevents post-procedural pain and also improves the regeneration of the squamous epithelium.²⁷ Thus, we recommend high dose proton pump therapy (e.g., pantoprazole 40 mg twice daily). This can also be combined with a sucralfate suspension 5 mL 3 to 4 times a day, as needed for 3 days after ablation. However, no patient in the study required sucralfate.

Follow-up for hybrid-APC is similar to that of standard APC- or RFA-treatment. After ablative treatment is completed, the first endoscopic follow-up should be performed at 3 months. If BE is found, patients need to undergo repeated ablative therapy and be re-assessed in 3-month intervals until the BE is completely removed. Patients are then followed up every 3 months for 1 year, 6 months for 1 year, and yearly thereafter.

The strengths of our study is that is a prospective evaluation of a novel treatment with long term follow-up. Our study has some limitations. Although it is a prospective study, it is a single centre, small-scale study which limits the generalisability of results. Our study was conducted in a tertiary centre with a high level of expertise in BE treatment which could explain the low rate of adverse events and high technical success that may not be observed in other settings. However, this could also be due to the small sample size and larger studies are certainly needed to confirm these findings. Two out of 11 patients had to be excluded from the study because we did not have a two-year follow-up. However, both of them were in remission when they stopped follow-up at 6 and 12 months, respectively.

In summary, we have demonstrated in this prospective pilot study that hybrid-APC appears promising in the treatment of BE with a tolerability and a safety profile comparable to RFA with

lower rates of post-procedure stricture formation. Furthermore, our study was the first to demonstrate a long-term efficacy of hybrid-APC. However, larger multi centre studies are required to confirm our findings.

Conflicts of Interest

Erbe (Tuebingen, Germany) sponsored 15 hybrid-APC probes for the study. Otherwise, no potential conflict of interest relevant to this article was reported.

Supplementary Materials

Supplementary data is available at <https://doi.org/10.18528/ijgii200050>.

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