Efficacy and one year follow up of argon plasma coagulation therapy for ablation of Barrett’s oesophagus: factors determining persistence and recurrence of Barrett’s epithelium

K K Basu, B Pick, R Bale, K P West, J S de Caestecker

Introduction: Barrett’s epithelium (BE) has malignant potential. Neither acid suppression nor antireflux therapy produce consistent or complete regression of the metaplastic epithelium. Endoscopic thermoablation with argon plasma coagulation (APC) offers a different approach but factors influencing its outcome have not been systematically examined.

Aim: To assess the efficacy of APC and factors influencing initial and one year outcome.

Methods: Fifty patients, mean age 61.4 years, mean BE length 5.9 cm (range 3–19), underwent APC therapy at four weekly intervals while receiving proton pump inhibitor (PPI) therapy. BE margins were marked by India ink tattooing and extent was documented by grid drawings, photography, and 2 cm interval quadrant jumbo biopsies. Twenty four hour ambulatory oesophageal pH studies were done while on PPIs before and after APC therapy, and Bilitec bilirubin monitoring after APC completion.

Results: A total of 68% of patients achieved >90% BE ablation after a median of four APC sessions. Persistent BE (>10% original BE area) was associated with longer initial BE length despite more APC sessions. Persistent acid and bile reflux on PPIs, although commoner in this group, were not significantly different from those successfully ablated. Fifteen of 34 patients (44%) with successful macroscopic clearance had buried glands, present in 8.3% of a total of 338 biopsies. At the one year follow up, only 32% of those with initial successful ablation showed no recurrence. BE recurred or increased in most with mean segment length increases of 1.1 cm and 1.6 cm, respectively, in patients with previous full ablation and those with persistent BE. The presence of buried glands did not predict BE recurrence. Patients who reduced their PPI dose had significantly greater BE recurrence.

Conclusions: APC is most effective for shorter segment BE ablation but “buried” glands do occur. Recurrence of BE is common at one year, especially in those with initial persistent and/or long segment BE and those who reduce their PPI dose.

Barrett’s epithelium (BE) is a premalignant condition secondary to severe chronic gastro-oesophageal reflux.1 Prospective endoscopic surveillance studies estimate the incidence of oesophageal adenocarcinoma at approximately 1:100 patient years.2 High risk factors include increasing length of BE,3,4 male sex,5 presence of dysplasia,6 and possibly duodenagastro-oesophageal reflux.7

Current management of BE includes endoscopic surveillance which remains contentious due to both the significant morbidity and mortality associated with oesophagectomy for high grade dysplasia or early adenocarcinoma8,9 and the lack of conclusive evidence of cost benefit. The aim of medical therapy is to reduce acid reflux using potent acid suppressant agents such as proton pump inhibitors (PPIs). Antireflux surgery is also advocated for reflux control, particularly for those with inadequate response or intolerance of pharmacological therapy. Unfortunately, neither of these approaches has been shown to induce consistent or complete BE regression.10-12

This has led to examination of new endoscopic thermoablative techniques in the setting of acid suppression.13 Argon plasma coagulation (APC) is an example of one such technique,14 which has advantages over laser therapy in being cheaper, more portable, and theoretically safer. The ultimate aim of this therapy is to reduce malignant potential which is related to the presence of BE. A number of studies have reported on the efficacy of APC for BE ablation15-17 however, follow up patient numbers are small and the long term stability of the resulting neosquamous epithelium remains unclear.

Our aims were therefore to assess the efficacy of APC for BE ablation and to investigate factors influencing the outcome of therapy and stability of the neosquamous epithelium after one year of follow up in a cohort of 50 patients.

PATIENTS AND METHODS

Patients

Patients were recruited from a local BE database. All had ≥ 3 cm of columnar lined oesophagus (with specialised intestinal metaplasia on histology) above the gastro-oesophageal junction which was defined endoscopically as the most proximal margins of the gastric longitudinal folds.18 Written informed consent in all and local ethics approval were obtained. Exclusions included those with serious comorbidity—that is, severe cardiac or respiratory disease—disseminated cancer, intolerance to endoscopy, inability to take PPIs, use of anticoagulants, steroids or regular non-steroidal anti-inflammatory drugs, history of previous gastro-oesophageal surgery, and any patient with confirmed or previous high grade dysplasia or oesophageal cancer.

Medication

All patients were established on PPI regimens, usually omeprazole 20 mg twice daily or lansoprazole 30 mg daily to

Abbreviations: BE, Barrett’s epithelium; PPI, proton pump inhibitor; APC, argon plasma coagulation.
achieve adequate acid suppression (assessed by 24 hour oesophageal pH measurement, see below) defined as the total time (24 hours) oesophageal pH was <4 less than 1.6% in concordance with normal values for controls on twice daily PPIs. In patients with acid reflux breakthrough, the PPI dose was increased to omeprazole 60 mg daily in divided doses.

Oesophageal studies
Prior to endoscopic ablation, all patients underwent standard oesophageal manometry followed by 24 hour ambulatory oesophageal pH monitoring (Synectics Medical Inc., USA) while on PPI therapy using an antimony pH catheter placed 5 cm above the manometrically located lower oesophageal sphincter. Where necessary the dose of PPI was increased as indicated above. The pH and manometry measurements were repeated at least six weeks after completion of APC ablation therapy; with the addition of 24 hour ambulatory oesophageal bilirubin monitoring (Bilitec 2000 system; Synectics Inc., USA) as a means of detecting duodenogastro-oesophageal reflux. The normal value for bile reflux was taken as per cent of time over 24 hours that absorbance was greater than 0.14 units.

BE extent
The proximal and distal margins of BE were marked using India ink tattooing during the first visit and extent was documented using endoscopic grid drawings and photography.

Histology
Quadrantic 2 cm interval jumbo biopsies were taken for histological confirmation of BE prior to ablation and at study completion to document normal squamous re-epithelialisation and look for evidence of “buried” BE glands. All samples were assessed by a single experienced dedicated histopathologist with a special interest in gastrointestinal histopathology (KPW).

Argon plasma coagulation (APC)
Endoscopy was performed on a day case basis using intravenous midazolam sedation (Hypnovel, Roche, Welwyn Garden City, Herts, UK; 2.5–10 mg), topical lignocaine spray (Xylocaine 10%; Astra, Kings Langley, Herts, UK), and hyoscine butylbromide (Buscopan, Boehringer Ingelheim, Bracknell, Berkshire, UK) 20–40 mg intravenously to inhibit oesophageal peristalsis. Pulse oximetry and blood pressure were recorded throughout the procedures. Using an Erbe APC 300 system (Erbe Medical UK Ltd, Leeds, UK) and Erbe gastrointestinal flexible probes, APC was delivered at a 30 watt setting at four weekly intervals aiming to treat one third of the oesophageal circumference per session until macroscopic clearance was achieved. For shorter segment BE and islands, point application was used and for larger areas longitudinal “stroking” of the probe in a caudal to cranial direction was employed to achieve a white coagulum thermal injury. Any patient symptoms were recorded and patients were contacted by telephone 24 hours post treatment to assess for complications. Failure of treatment was arbitrarily defined as ≥10% of the original Barrett’s area persisting despite ablative treatment to that area on at least two occasions. Thus where it was clear after two sessions that no squamous re-epithelialisation had occurred, the patient was deemed a treatment failure. Patients in whom some effect was noted continued in the study to a maximum of eight sessions (see results below) after which the final area of residual BE was calculated.

One year follow up
Patients and their general practitioners were instructed to continue the same dose of PPIs used during the study and underwent endoscopic review at one year following completion of treatment during which BE extent, if any, was reredocumented and biopsies taken from the previous original levels for histological examination. Medication at follow up was reviewed based on self reporting.

Statistics
The effects of persistent acid reflux, bile reflux, initial extent of BE segment length, and patient age on initial efficacy of APC therapy were compared. The presence of BE recurrence after one year of follow up was also examined in relation to the previous efficacy of ablation, presence of buried glands, degree of acid and bile reflux, and change in PPI dose. The Mann-Whitney U test (adjusted for ties with two sided p values) and Fisher’s exact test were used as appropriate (Arcus Quickstat Biomedical, Cambridge Sciences Park, Cambridge, UK version 1.1).

RESULTS
Initial efficacy of APC ablation
Fifty patients completed a course of APC ablation therapy after a median of four sessions (range 1–8). Mean age was 61.4 years (SD 11.5, range 28–80). Mean BE length was 5.9 cm (SD 3.1, range 3–19). Thirty four (68%) patients achieved ≥90% BE clearance (30 with 100% clearance) and 16 patients had persistent BE; most of these achieved at least 50% ablation. Squamous re-epithelialisation was confirmed histologically in all patients. “Buried” BE glands occurred in 15 of 34 patients (44%), with successful macroscopic clearance representing 28 of 338 biopsies (8.3%). Nine of 16 (56%) patients with persistent BE had “buried” glands in six of 133 biopsies (19.5%). Overall “buried” glands occurred in 34 of 471 biopsies (11.5%) in 24 (48%) patients.

Safety of APC ablation
APC was well tolerated using minor sedation. Mean duration of APC application was 9.1 minutes (range 1–20). Side effects were self limiting and comprised central chest discomfort after 32% of APC sessions, odynophagia after 25%, and temporary dysphagia associated with superficial ulceration after 4%. No interventions were required. No strictures or bleeding occurred.

<table>
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<th>Table 1</th>
<th>Persisting acid reflux after argon plasma coagulation (APC) therapy for Barrett’s epithelium (BE) ablation</th>
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<tr>
<td>APC outcome</td>
<td>Mean (SD) age (y)</td>
</tr>
<tr>
<td>Successful ablation (n=34)</td>
<td>60.6 (10.9)</td>
</tr>
<tr>
<td>Persistent BE (n=16)</td>
<td>63.2 (12.9)</td>
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<td>IQR, interquartile range. *p&lt;0.0001, **p&lt;0.014.</td>
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Factors affecting squamous re-epithelialisation after APC ablation (tables 1, 2)

Persistent BE (n=16) was associated with longer initial BE segment length despite more APC sessions. Most had persistent tongues but six patients had greater than 50% of their circumferential BE persisting. There was a tendency for persistent acid and bile reflux to be commoner in this group although statistical significance was not achieved. As assessed by oesophageal pH monitoring at completion of APC therapy, only two patients had “pathological” acid reflux, defined as per cent daytime pH less than 4 exceeding 8.2% and/or night time acid reflux exceeding 3%.19 Bile reflux exceeded the normal range in 87% of patients despite PPI therapy.

One year follow up after APC (table 3)

All 50 patients attended for endoscopic follow up after a mean of 14 months post APC treatment. A mean of 1.1 cm BE segment length recurrence was seen in patients with initial BE clearance compared with a mean of 1.6 cm increase in BE segment length in those with persistent BE at the end of APC therapy (p=0.06). Only 11 of 34 patients with initial total eradication of BE (32%) had no recurrent BE at follow up.

Effect of “buried” glands on BE recurrence at one year

Patients with macroscopic clearance and no histological evidence of “buried” glands had a similar BE recurrence rate at one year compared with those with macroscopic clearance and buried glands (table 4). There were no significant differences in age, initial BE length, time of follow up, or degree of acid suppression between the two subgroups. At one year of follow up, “buried” glands occurred as a new finding in two of 19 previously clear patients, representing four (2%) of 185 biopsies, and persisted in six of 15 patients with previous buried glands, representing 14 (9%) of 148 biopsies.

Effect of reducing study PPI dose at one year (table 5)

Contrary to recommendations, 12 patients reduced their study PPI dose to omeprazole 20 mg once daily or less. These patients had a significantly greater incidence of BE recurrence compared with those remaining on higher dose therapy.

DISCUSSION

APC ablative therapy proved to be safe and well tolerated, with only minor self limiting side effects. In particular, no strictures occurred, perhaps reflecting our policy of avoiding circumferential treatment in any one treatment session. Nearly 70% of patients achieved successful macroscopic ablation in keeping with other study findings;15 however, buried glands were seen in a high proportion (44%) of this group at histology. This may have resulted from the low energy settings used in our study. Recently, some workers23 have addressed this issue by adopting higher power APC settings to achieve more complete

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<th>Table 2 Bile reflux in 31 Barrett’s epithelium (BE) patients after argon plasma coagulation (APC) therapy</th>
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<tr>
<td>APC outcome</td>
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<tr>
<td>Successful ablation (n=23)</td>
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<tr>
<td>Persistent BE (n=8)</td>
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Not all patients were willing/able to undergo Bilitec monitoring. *p<0.0001; **p=0.01.

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<th>Table 3 Comparison of Barrett’s epithelium (BE) recurrence at one year between patients with successful macroscopic versus those with persistent BE after argon plasma coagulation (APC) ablation</th>
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<tr>
<td>APC outcome</td>
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<tr>
<td>Successful ablation (n=34)</td>
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<td>Persistent BE (n=16)</td>
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Values are mean (SD).

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<th>Table 4 Outcome of successful argon plasma coagulation (APC) macroscopic ablation in patients with and without buried glands at one year</th>
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<tr>
<td>Successful ablation (n=34)</td>
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<tr>
<td>Buried glands not present (n=19)</td>
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<td>Buried glands (n=15)</td>
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BE, Barrett's epithelium; FU, follow up; IQR, interquartile range.

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<th>Table 5 Effect of reducing proton pump inhibitor (PPI) dose on Barrett’s epithelium (BE) recurrence one year after argon plasma coagulation ablation</th>
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<td>No of patients on study dose PPI medication</td>
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<td>BE recurrence (cm)</td>
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<td>&gt;1.5</td>
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Fisher’s exact test p=0.01.
and potentially deeper ablation. This resulted in increased success in histological as well as macroscopic clearance of BE at the expense of more procedure related morbidity. A substantial minority (n=16) failed therapy which we defined as ≥10% of the original Barrett’s area persisting despite ablative treatment to that area on at least two occasions. Most treatment failures had persistent tongues but six patients had greater than 50% of their circumferential BE persisting. These patients had significantly longer mean initial BE segment length and a tendency to greater acid and bile reflux on PPI therapy. Bile reflux, a marker of duodenogastro-oesophageal reflux, was common and exceeded normal established values in the majority of patients with or without successful macroscopic clearance after APC therapy at one year of follow up. Furthermore, the finding of buried glands at completion of APC did not appear to influence the likelihood of BE recurrence at one year.

In summary, initial longer segment length, persistent BE at completion of APC therapy, and reduction in PPI dose are associated with more BE recurrence one year after APC ablation therapy. The importance of bile reflux, although common, is less clear. Buried glands do not affect outcome at one year. Thus BE ablation is feasible but recurrence is common at one year. More aggressive ablation therapy may be effective but the risk/benefit ratio in terms of earlier risk reduction versus side effects remains to be established. Nevertheless, we do not advocate APC intervention for patients with uncomplicated Barrett’s mucosa and at present the only clinical indication for this possible form of intervention is established dysplasia, although even this remains experimental as long term follow up data have yet to be reported. This study has looked at the feasibility and durability of this technique. The relevance to clinical practice will emerge when biological markers to select those patients at high risk of developing dysplasia and carcinoma are identified.

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