Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
183
JNMU
Journal of Nanjing Medical University, 2009, 23(3):183-188
www.elsevier.com/locate/jnmu
Research Paper

Endoscopic ablation of Barrett's esophagus using the second generation argon plasma coagulation: a prospective randomized controlled trail ☆

Li Zhang[a], Lei Dong[a,*], Jia Liu[b], Xiaolan Lu[a], Jun Zhang[a]

[a]*Department of Digestive Disease, the Second Affiliated Hospital, Medical School of Xi' an Jiaotong University; Xi' an 710004, China;*
[b]*Department of Orthopedics, the Second Affiliated Hospital, Medical School of Xi' an Jiaotong University; Xi' an 710004, China*

Received 10 November 2008

Abstract

Objective: To investigate the efficacy and safety of the second generation argon plasma coagulation(VIO APC) in the ablation of Barrett's Esophagus. **Methods:**A total of 35 patients with uncomplicated Barrett's esophagus entered into a prospective, randomized, unblinded study comparing the treatment VIO APC combined with a proton pump inhibiter with a proton pump inhibiter administered alone. VIO APC was performed at a power setting of 40W, and argon gas flow at 1.5-2.0 L/min, and "forced" mode. Ablative treatment was repeated until either no Barrett's epithelium remained or a maximum of 5 treatment sessions occurred. **Results:**In the ablation group, macroscopic complete ablation was achieved in 14 of 18 patients, and complete ablation confirmed by histology in 12 of 18 patients ($P < 0.01$). Buried glands were observed in 2 patients who had achieved macroscopic ablation. The Barrett's mucosa averaged a reduction of 65%(range 50-75%) in the remaining 4 patients. In the control group, only 2 patients had partial regression, median 30%(range 20-40%). In the ablation group, post-treatment 4 patients had transient retrosternal pain, and 3 patients had mild epigastric discomfort. One patient had a small hemorrhage during the procedure, which ceased after norepinephrine and thrombosin were administered through the endoscope biopsy channel. No adverse events were observed in the control group. During 11.8(4-15) months follow-up, patients who had achieved the complete ablation have no evidence of relapse of Barrett's esophagus. **Conclusion:**VIO APC with a relatively low power setting can effectively ablate the Barrett's mucosa. No severe adverse events were observed. Long-term follow-up is needed to assess cancer prevention and the durability of the neo-squamous epithelium.

Keywords: Barrett's esophagus; argon plasma coagulation; efficacy; safety

INTRODUCTION

Barrett's esophagus is a complication of gastro-esophageal reflux disease, in which the normal squamous epithelium at the lower segment of the esophagus is replaced by columnar epithelium with specialized intestinal metaplasia. Histologically, it is characterized by the existence of goblet cells[1,2]. As a premalignant condition of esophageal adenocarcinoma, patients with Barreett's esophagus are 30 times likely to develop esophageal adenocarcinoma than the general population[3,4].

Endoscopic ablation therapy is the method that intentionally causes an acute lesion of the mucosa, destroying the metaplastic columnar epithelium. Recovery of the squamous epithelium in an acid-reduced environment may then follow. Several ablation techniques have been used including, thermal laser photoablation, multipolar electrocoagulation, endoscopic mucosa resection, photodynamic therapy(PDT) and argon plasma coagulation(APC)[5,6]. APC transfers electrical energy to the tissue, without contact with the tissue, by means of an ionized electrically conducting plasma of argon gas, delivered at between 1 and 2 L/min.

☆ This work was supported by Major Project of Clinical Subjects of Hospitals Afjiliated to the Ministry of Health(2007353).
*Corresponding author.
E-mail address: donglei4488@sina.com

The argon plasma causes very high temperatures on the surface, producing a zone of devitalisation, surrounded by zones of coagulation, desiccation, and tissue shrinkage. Then the tissue looses its electric conduction and the plasma beam changes its direction. Therefore, the depth effect should be limited and full thickness necrosis and perforation are unlikely to happen[7-9]. APC may have advantages over other ablative modalities. The equipment is inexpensive, easy to use, and does not require a laser. In contrast to PDT, there is no need to administer a photosensitizing drug, and systemic photosensitization is avoided. But there are still some disputes on the efficacy and safety of the treatment of Barrett's esophagus using APC.

Second-generation argon plasma coagulation(VIO APC) with its modes 'forced','pulsed', and 'precise' is a further development of the ICC/APC 300 system(first-generation APC, standard APC). In comparison to standard APC, it offers a broadened bandwidth of settings including different APC modes and a range of power settings from 1 to 120 W. In the study by Manner and colleagues[10], fundamental data on the characteristics of the various APC modes and clinical data from more than 600 patients treated in two high-volume endoscopy centers were analyzed. Using the various modes of APC in a variety of gastrointestinal diseases, including Barrett's esophagus, minor complications were observed in 9-21% of patients. Major complications occurred in 1-7% of patients. The data on the use of the second generation of APC-VIO APC is still very limited.

MATERIALS AND METHODS

Subjects

Patients with uncomplicated Barrett's esophagus were enrolled in the study. Written informed consent was obtained from all study patients who were thoroughly informed about the aim and process of the study. The study protocol and consent were approved by the ethics committee of Xi'an Jiaotong University. Including criteria were: confirmed endoscopic and histopathologic diagnosis of Barrett's esophagus without evidence of adenocarcinoma; patients who were enrolled in the trial understood Chinese and were allowed to quit at any phase of the study.

Excluding criteria were:the patients had proof of existing, or a low or high potential for malignancy of intraepithelial neoplasm, or esophageal adenocarcinoma; patients had undergone any endoscopic treatments; the existance of esophageal varices; patients had undergone any esophageal or gastric operation(including esophagectomy, Billroth I or Billroth II operation, vagus nerve mutilation, fundoplication, gastrectomy); younger than 18 or older than 80 years of age and had any uncontrolled co-morbidities. Other excluding criteria were related to the treatments. They were allergic to proton pump inhibiter, uncontrolled blood coagulation dysfunction and allergic to coumarins or heparin. Uncontrolled coagulation dysfunction includes plasmozyme activity less than 50% and blood platelets count less than 50×10^9/L.

Chromoendoscopy and biopsy

Upper endoscopy was performed by using PENTAX EG-2901 endoscope. Following the standard endoscopy, chromoendoscopy was carried out in the same examination with the instillation of 8ml of 2% Lugol's solution, directly by the biopsy channel of the endoscope, from the esophagogastric junction to the lower one third of esophagus. Normal esophageal mucosa presented as a homogenous dark brown or greenish brown color, while the Barrett mucosa remained unstained(***Fig. 1***). The length of the Barrett's segment was measured from gastroesophageal junction to the distal end of the Barrett segment. Patients with erosive esophagitis were asked to return for endoscopy after one further month of treatment with the proton pump inhibitor. If there was no endoscopic evidence of esophagitis, the following endoscopic landmarks were determined and were recorded in centimeters from the incisor teeth by using markings on the endoscope: the proximal-most squamocolumnar junction, including Barrett's islands, and the gastroesophageal junction.

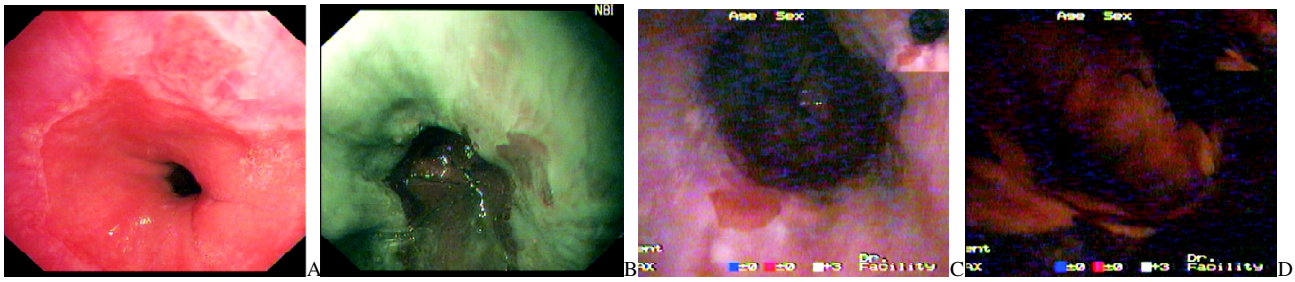
Four-quadrant biopsy specimens were obtained at least every 2 cm from the gastroesophageal junction proximal to the squamocolumnar junction. In addition, biopsy specimens were taken from any endoscopic "target" lesion(e.g., ulcer, nodule, polyp) in the Barrett's segment. All specimens were soaked in 10% paraformaldehyde and were processed and sectioned in a single laboratory by an unkown pathologist. The slides were stained with hematoxylin and eosin. The histopathologic diagnosis of Barrett's esophagus was defined by the presence of specialized intestinal metaplasia in specimens taken proximal to the gastroesophageal junction. Dysplasia was defined as neoplastic epithelium confined within the basement membrane in the absence of inflammation and was classified as:negative for dysplasia, low-grade dysplasia, high-grade dysplasia and carcinoma.

Treatments

Computer-generated randomization was done to allocate patients to the APC group or the control group.

APC protocol

Conscious sedation was obtained with an intramuscular injection of diazepam and the beginning of the procedure was preceded by local pharyngeal anesthesia



A:Endoscopic view of Barrett's island above the gastro-esophageal junction; B:Chromoendoscopic view of Barrett's island(unstained area) above the gastro-esophageal junction; C:Endoscopic view of Barrett's tongue above the gastro-esophageal junction; D:Chromoendoscopic view of Barrett's tongue above the gastro-esophageal junction, in the unstained area, residual normal squamous epithelium(stained area) can still be observed.

Fig. 1 Chromoendoscopy with Lugol's solution of Barrett's esophagus

with xylocaine spray. In some cases, intramuscular injection of anisodamine was given to prevent peristaltic esophageal contractions during the test, APC was done using the ERBE VIO 200D Argon beamer(ERBE Medical,Tubingen, Germany). The argon beam instrument consists of a flexible Teflon catheter which passes through the endoscope instrument channel, an argon gas source and an electrosurgical unit. APC was applied until a white coagulum appeared at a power setting of 40W and argon gas flow of 1.5-2.0 L/min, and "forced" mode. Ablation was initiated at the gastro-esophageal transition zone defined as the end of the gastric folds and the beginning of the tubular esophagus and preceded proximally(oral) to the squamocolumnar junction in a longitudinal brush-like stroking fashion. To reduce the risk of stricture formation, treatment was limited in any single procedure to 50% of the circumference of long segment of Barrett's esophagus. Endoscopic treatment sessions were continued at 4-to 6-week intervals until there was no endoscopic evidence of Barrett's esophagus or a total of 5 treatment sessions had occurred.

After the procedures, patients were admitted to the gastroenterology ward and treated with oral omeprazole (20 mg twice a day). Any treatment related symptoms, including dysphagia, odynophagia, and chest pain were noted. Patients were discharged in three days and administered oral high-dose proton pump inhibitor until the ablation was completed in 3 months.

All patients randomized to control group were simply treated with oral high-dose proton pump inhibitor for 3 months.

Follow-up

Follow-up endoscopies and biopsies were done at 3 months, 6 months and 12 months. During follow-up endoscopies, the length of any residual Barrett's segment was noted and four-quadrant biopsies were taken from the previous sites.

Statistical analysis

Statistical analysis was performed using SPSS13.0 (SPSS Inc., Chicago,IL, USA). Patients' age and the length of Barrett's esophagus were compared using Mann-Whitney U tests. Patients' gender, histology of Barrett's esophagus, complaints before treatment and results of treatments were compared using Fisher exact test. Differences were considered statistically significant if $P < 0.05$.

RESULTS

From May 2007 to June 2008, 84 patients were macroscopically diagnosed with Barrett's esophagus, of which 36 patients had the diagnosis confirmed by histology. Squamous re-epithelialization after biopsy excision of Barrett's mucosa occurred in one patient. It was a 0.3x0.3 cm Barrett's island above the squamocolumnar junction. Two biopsy specimens were taken from the area, and were confirmed as Barrett's esophagus by histology. Thirty-five patients were randomized to the ablation group or the controlled group (***Table 1,2***). The results of treatments were summarized in ***Table 3***.

In the ablation group, twenty-four treatment sessions were performed in all the patients. The median number of treatment sessions was 1.3(1-3), and 66.7%(12/18) patients achieved macroscopic complete ablation only after one session(***Fig. 2***). Post-treatment, 4 patients had transient retrosternal pain, and 3 patients had mild epigastric discomfort. One patient had a small haemorrhage during the procedure, which ceased after norepinephrine and thrombosin were administered through the endoscope biopsy channel. No esophageal stricture or other severe adverse events was observed. In the controlled group, no side effects were observed. During the follow-up endoscopies, the patients who had achieved the complete ablation have no evidence of relapse of Barrett's esophagus.

DISCUSSION

The prognosis of esophageal adenocarcinoma has always been bad, with the median survival of only 0.9

Table 1 **Demographic data and endoscopic findings of the two patients group**

	Ablation group(n = 18)	Control group(n = 17)
Age, years, median(range))	55(31-75)	53(34-67)
Gender(male: female)	12:6	10:7
Length of Barrett's esophagus, cm, median(range))	2.1(1.0-4.0)	2.5(1.5-5.0)
Hiatal hernia	2	1
Histology of Barrett's esophagus		
No dysplasia	18	17
Low grade dysplasia	1	0
Median follow-up(months)	12(4-15)	12(4-16)

No significant differences were observed between the two groups.

Table 2 **Main complaints before ablation in the two patients groups**

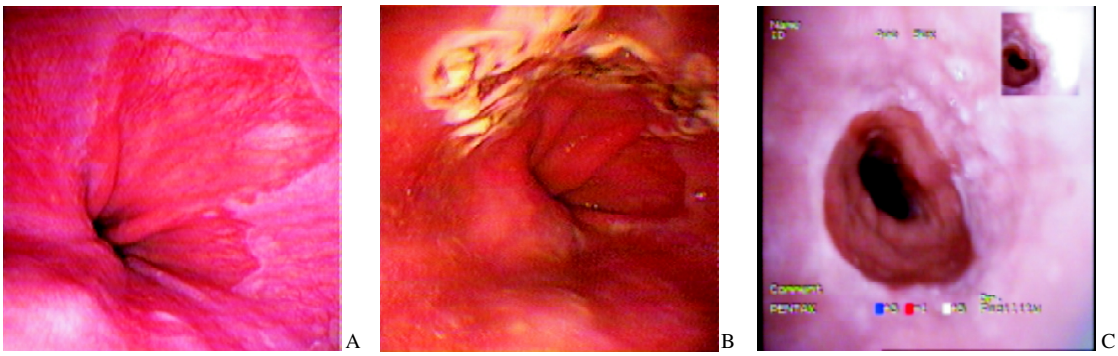
	Ablation group n = 18	Control group n = 17
Upper abdominal pain	12	10
Sour regurgitation	14	13
Dysphagia or odynophagia	7	8

No significant differences were observed between the two groups.

Table 3 **Followed-up endoscope findings of the two groups**

	Ablation group	Controlled group
Endoscopic complete regression	14*	0
Partial regression	4**	2△
Buried gland	2	0

*Fisher exact test:$P < 0.01$; **partial regression, median 65%(range 50-75%);△ partial regression, median 30%(range 20-40%).



A B C

A:Endoscopic view of Barrett's tongue above the gastro-esophageal junction; B:Endoscopic view of white coagulation after the APC treatment; C:One month after APC session and treatment with omeprazole, the endoscopic view of squamous re-epithelialization at the lower part of esophagus

Fig. 2 The ablation of Barrett's esophagus using VIO APC

years. Many scientists try to reduce the risk of esophageal adenocarcinoma by treating its premalignant condition-Barrett's esophagus, in an attempt to reduce the death rate. Data showing that either pharmacologic or anti-reflux surgical therapy lead to significant regression of Barrett's esophagus are sparse; hence, there is considerable interest in ablation therapy[11].

In the prospective study of Pinotti *et al*[12], the ablation rate of Barrett's mucosa was 100%. In the study of Pagani *et al*[13], the complete ablation rate was 72.34%. Several controlled randomized clinical trials on the endoscopic ablative therapy of Barrett's esophagus have been completed around the world[14]. Among them only the studies of Ackroyd *et al*[15,16] and Bright and colleagues[17] compared APC with placebo. Other studies compared APC with other ablative therapy[18-22], but rarely do we see any reports of VIO APC. In the study of Ackroyd *et al*[15], at the 1-year follow-up, the ablation rate in the standard APC group was 63%, and 15% in the control group.($P < 0.01$) In the present trial, complete ablation confirmed by histology was achieved in 12 of 18 patients(66.7%,), and 65% ablation was achieved in the remaining 4 patients. We can conclude that VIO APC has a similar efficacy in the treatment of Barrett's esophagus to standard APC.

A drawback of all forms of ablative therapy is the persistence of columnar glands beneath the neosquamous epithelium. The depth of the thermal effect depends on three factors:the power setting, the duration of application, and the distance from the probe tip. Higher power leads to deeper tissue damage, lesser incidence of columnar glands with intestinal metaplasia buried under the neo-squamous epithelium[23]. But high ablation power may lead to esophageal stricture and perforation[24]. The popular power setting of APC varies from 30W to 90W. Basu and colleagues[25] used a 30W(low power) APC setting to deliver therapy to 50 Barrett's esophagus. Buried glands were observed in 15 of the

34 patients(44%) with successful macroscopic clearance and in nine of the 16 patients(56%) with persistent Barrett's esophagus. No strictures or bleeding were reported. Manner *et al*[26] treated 60 patients with standard APC at a power setting of 90W(high power), and 77% of patients showed complete response (histological and macroscopic complete ablation), complications occurred in 9.8%(5/51) of patients, including 2 hemorrhages that needed therapeutic endoscopy, 2 esophageal stricture that needed bouginage, and 1 perforation that healed after expectant treatment. Another study of Manner *et al*[26] demonstrated VIO APC had stronger coagulation effects than standard APC. In the present trail, the power setting of VIO APC was only 40W, no occurrence of severe adverse events was observed; and buried glands were observed barely in 11% patients. So we think the relatively low power setting of VIO APC is appropriate.

The relapse of Barrett's mucosa is a common problem that has bothered endoscopists. The studies across the world all mention the incidence of relapse. In the study of Basu and colleagues[25], only 11 of the 34 successful treatment cases(32%) had no macroscopic Barrett's esophagus recurrence. In the study of Pinotti *et al*[12], at 17-month follow-up, the recurrence of Barrett's esophagus was observed in 1 of the 19 patients who underwent standard APC. In the study of Ackroyd *et al*[22] and Bright *et al*[16], the results were much more encouraging. After being followed-up for 68 months, 70%(14/20) patients still had a 95% ablation rate, and 57%(8/14) patients showed no evidence of Barrett's esophagus either by macroscopy or histopathology. In the present trail, the result was quite encouraging. The median follow-up time was 11.8 months(the longest one was 15 months). No relapse of Barrett's mucosa was observed in the patients who had achieved complete ablation. But to determine whether the regression can be maintained for a long time will require further follow up.

Complications of APC can be divided into major complications and minor complications. The former mainly includes hemorrhage, perforation and stricture, and the latter includes pain, dysphagia, odynophagia, epigastric discomfort, fever, and so on. Perforation is related to the APC output power, which has discussed above. To reduce the risk of esophageal stricture, the ablation area was limited to one half or two third of the circumference in one session in most clinical trails[14,15,22-26]. In the present trail, we also limited the ablation area to one half of the circumference, and no stricture was observed. In the present trail, during the procedure, small amount of hemorrhage occurred in one patient. The reason might be that the distance from probe tip to the tissue surface was too close, which led to contact coagulation. In some studies[14, 16-18], the retrosternal pain and upper gastrointestinal discomfort of some patients were so severe, that analgesic and and/or anti-emetic medications were required. In the present study, the complications were mild; except for proton pump inhibitor, no medications were administered.

On the whole, VIO APC with a relatively low power setting can effectively ablate the Barrett's mucosa with special intestine metaplasia, and make it regress to the squamous epithelium without severe adverse effects, as well as standard APC. But to determine whether this technique will result in a lasting regression effect and reduce the morbidity of esophageal adenocarcinomas, will require clinical trails with large samples and a long follow-up.

References

[1] Slehria S, Sharma P. Barrett esophagus. *Curr Opin Gastroenterol* 2003; 19:387-93

[2] Gerson L B,Shetler K,Triadafilopoulos G. Prevalence of Barrett's esophagus in asymptomatic individuals. *Gastroenterology* 2002; 123:461-7.

[3] Solaymani-Dodaran M,Logan RF,West J,Card T,Coupland C. Risk of oesophageal cancer in Barrett's oesophagus and oesophageal reflux. *Gut* 2004; 53:1070-4.

[4] Kosuri K,Jankowski J. Adenocarcinoma in Barrett's esophagus, too common, too fatal, and still too badly managed. *J Clin Gastroenterol* 2007; 41:S129-S34.

[5] Kenneth K,Wang M D. Mucosal ablation therapy of Barrett's esophagus. *Mayo Clinic Proc* 2001; 76: 433-7.

[6] Barr H, Stone N, Rembacken B. Endoscopic therapy for Barrett's esophagus. *Gut* 2005; 54:875-84.

[7] Van Laethem JL, Cremer M, Peny MO, Delhaye M, Devière J. Eradication of Barrett's mucosa with argon plasma coagulation and acid suppression: immediate and mid term results. *Gut* 1998; 43: 747-51.

[8] Barham CP, Shepherd N, Barr H. Regression of Barrett's epithelium using argon gas coagulation and acid suppression. *Gut* 1996; 39:114.

[9] Odze RD, Lauwers GY. Histopathology of Barrett's esophagus after ablation and endoscopic mucosal resection therapy. *Endoscopy* 2008; 40:1008-15.

[10] Manner H, Enderle MD, Pech O, May A, Plum N, Riemann JF, *et al*. Second-generation argon plasma coagulation: two-center experience with 600 patients. *J Gastroenterol Hepatol* 2008; 23:872-8.

[11] Wani S, Sharma P. The role of chemoprevention in Barrett esophagus and esophageal adenocarcinoma. *J Clin Gastroenterol* 2007; 41:S135-S40.

[12] Pinotti AC, Cecconello I, Filho FM, Sakai P, Gama-Rodrigues JJ, Pinotti HW. Endoscopic ablation of Barrett's esophagus using argon plasma coagulation:a prospective study after fundoplication. *Dis Esophagus* 2004; 17: 243-6.

[13] Pagani M, Granelli P, Chella B, Antoniazzi L, Bonavina L, Peracchia A. Barrett's esophagus: combined treatment using

argon plasma coagulation and laparoscopic antireflux surgery. *Dis Esophagus* 2003; 16, 279-83.

[14] Faybush, EM, Sampliner RE. Randomized trials in the treatment of Barrett's esophagus. *Dis Esophagus* 2005; 18, 291-7.

[15] Ackroyd R, Tam W, Schoeman M, Devitt PG, Watson DI. Prospective randomized controlled trial of argon plasma coagulation ablation vs. endoscopic surveillance of patients with Barrett esophagus after antireflux surgery. *Gastrintest Endosc* 2004; 59: 1-7.

[16] Ackroyd R, Wijnhoven B, Astill D, Watson D, Bright TF. HP22 Five year results of a prospective randomized controlled trail of argon plasma coagulation vs. endoscopic surveillance of patients with Barrett's esophagus after antireflux surgery. *ANZ J Surg* 2007; 77: A45.

[17] Bright T, Watson DI, Tam W, Game PA, Astill D, Ackroyd R, *et al*. Randomized trial of argon plasma coagulation versus endoscopic surveillance for Barrett esophagus after antireflux surgery: late results. *Ann Surg* 2007; 246:1016-20.

[18] Ragunath K, Krasner N, Raman VS, Haqqani MT, Phillips CJ, Cheung I. Endoscopic ablation of dysplastic Barrett's oesophagus comparing argon plasma coagulation and photodynamic therapy: a randomized prospective trial assessing efficacy and cost-effectiveness. *Scand J Gastroenterol* 2005; 40:750-8.

[19] Kelty CJ, Ackroyd R, Brown NJ, Stephenson TJ, Stoddard CJ, Reed MW. Endoscopic ablation of Barrett's oesophagus: a randomized-controlled trial of photodynamic therapy vs. argon plasma coagulation. *Aliment Pharmacol Ther* 2004; 20: 1289-96.

[20] Hage M,Siersema PD,van Dekken H, Steyerberg EW, Haringsma J, van de Vrie W, *et al*. 5-aminolevulinic acid photodynamic therapy versus argon plasma coagulation for ablation of Barrett's oesophagus: a randomised trial. *Gut* 2004; 53: 785-90.

[21] Sharma P, Wani S, Weston AP, Bansal A, Hall M, Mathur S, *et al*. A randomised controlled trial of ablation of Barrett's oesophagus with multipolar electrocoagulation versus argon plasma coagulation in combination with acid suppression: long term results. *Gut* 2006; 55:1233-9.

[22] Dulai GS, Jensen DM, Cortina G, Fontana L, Ippoliti A. Randomized trial of argon plasma coagulation vs. multipolar electrocoagulation for ablation of Barrett's esophagus. *Gastrointest Endosc* 2005; 61:241-2.

[23] Malick KJ. Clinical applications of argon plasma coagulation in endoscopy. *Gastroenterol Nurs* 2006; 29:386-91; quiz 392-3.

[24] Deviere J. Argon plasma coagulation therapy for ablation of Barrett's oesophagus. *Gut* 2000, 51:763-4.

[25] Basu KK, Pick B, Bale R, West KP, de Caestecker JS. 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. *Gut* 2002; 51: 776-80

[26] Manner H, May A, Rabenstein T, Pech O, Nachbar L, Enderle MD, *et al*. Prospective evaluation of a new high-power argon plasma coagulation system(hp-APC) in therapeutic gastrointestinal endoscopy. *Scand J Gastroenterol* 2007; 42: 397-405.

[27] Manner H, May A, Faerber M, Pech O, Plum N, Ell C. The tissue effect of second generation argon plasma coagulation (VIO APC) in comparison to standard APC and Nd:YAG laser in vitro. *Acta Gastroenterol Belg* 2007; 70:352-6.