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Role of argon plasma coagulation in treatment of esophageal varices

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Abstract

With the development of endoscopic therapy, argon plasma coagulation (APC) has been widely used by endoscopists. It has many advantages, such as simple to operate, low cost, and minimal invasiveness. Because of its capability of lesion ablation and hemostasis, APC has several indications in the gastrointestinal tract. One of them is esophageal varices. The aim of this review is to summarize the research on APC in this field to provide a reference for clinical practice.

Key Words: Esophageal varices; Argon plasma coagulation; Clinical practice; Endoscopic therapy; Gastrointestinal tract; Minimally invasive

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Core Tip: Considering the current relevant research results, argon plasma coagulation has considerable efficacy and safety in the treatment of esophageal varices.

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INTRODUCTION

Cirrhosis and portal hypertension can cause varicose veins in different parts of the digestive tract, of which esophageal varices (EV) are most common. EV occur in 5% of cirrhotic patients without varicose veins after 1 year and 28% after 3 years, while 12% of patients with mild EV after 1 year and 31% after 3 years will progress to severe EV. It can be seen that during the process of liver cirrhosis, 50%-60% of patients will have EV^[1-3]. EV rupture hemorrhage is a common clinical critical illness and is featured as sudden onset, large amount of bleeding, rapid progression, and high mortality. It is a potentially fatal complication in patients with liver cirrhosis and the mortality rate is as high as 20%^[3,4]. For patients with cirrhosis who have not been treated after diagnosis of EV, about 1/3 of patients would bleed for the first time in 2 years, of whom about 60% would re-bleed within 2 years^[5]. There are many hepatitis patients in China and cirrhosis combined with EV rupture bleeding seriously affects the prognosis of patients, causing a great psychological and economic burden on individuals, families, and society.

Upper gastrointestinal endoscopy is a preferred method for the diagnosis of EV rupture bleeding. Endoscopic treatment is also the main method for emergency hemostasis and prevention of re-bleeding in EV rupture. At present, the main methods of endoscopic treatment of EV included endoscopic variceal ligation (EVL), endoscopic injection sclerotherapy (EIS), and a combination of EVL and EIS. However, the recurrence rate after EVL was 21.3%-92% and the recurrence rate after EIS was 11%-24%. The traditional approach is to administer β -blockers after endoscopic treatment to reduce the recurrence of varicose veins, thereby reducing the rate of re-bleeding. However, some patients cannot tolerate or respond poorly to drugs, or have contraindications to use. For small EV, it is often impossible to perform effective ligation or sclerosis, so that varicose veins cannot be completely eradicated. Among the causes of EV recurrence, in addition to the persistent portal hypertension, failure to achieve complete eradication is also an important reason. In order to reduce recurrence and the bleeding rate, some guidelines emphasize that for varicose veins, complete eradication is possible, that is, after the basic eradication, the remaining small blood vessels are treated to achieve complete eradication, delay the recurrence of varicose veins, and further reduce the risk of bleeding as well as improve long-term efficacy.

At present, treatment methods for small and residual EV included endoscopic argon plasma coagulation (APC), photodynamic therapy, metal clip therapy, ligation, and additional sclerosis. Photodynamic therapy is a method for treating target tissues based on the cytotoxic effect of the photodynamic response of the photosensitizer. Its operation is cumbersome and costly and requires to be under dark for 3-7 d after treatment. Metal clip therapy uses metal clamps to clamp the small veins under the guidance of endoscopy and has a certain effect on the occlusion of the small veins, but the action site is limited with a risk of damaging the blood vessels. For the small tortuous residual small veins, it is often impossible to perform effective ligation or hardening and there is a risk of esophageal stenosis. Therefore, in clinical practice, the above methods are subject to certain restrictions. More and more studies have shown that treatment of EVs ≤ 0.3 cm by APC can promote mucosal fibrosis, and inhibit capillary hyperplasia and invasion of perforating veins, thereby reducing the recurrence of varicose veins and achieving complete eradication.

APC belongs to monopolar electrosurgery and is characterized by non-contact thermal coagulation. It uses argon gas, which is stable, non-toxic, and odorless inert. Under the action of high frequency electricity, the argon gas is ionized into an argon plasma beam. Then, the high-frequency current was applied to target tissue to achieve coagulation and a uniform and stable hemostatic effect. Based on its technical principle, APC generator usually has two main parts. One part is for argon and the other is for high frequency electricity. Due to its wide function, superficiality, easy operation, safety, and effectiveness, APC has been widely used in many gastrointestinal diseases, such as early cancer of the digestive tract, precancerous lesions, Barrett's esophagus, dilatation of the gastric antrum, and non-varicose gastrointestinal bleeding^[6-10]. The depth of APC treatment is generally 0.5-3.0 mm and it can seal blood vessels with a diameter of ≤ 0.3 cm, therefore it is reported that APC can also play a role in the treatment of EV. Nakamura *et al*^[11] treated EV using APC the first time. Since esophageal mucosal fibrosis is the key to the prevention of EV recurrence, subsequent studies will use APC as an adjunct to the combination of EVL and/or EIS to eradicate EV^[3,12].

The operation process of APC in the treatment of EV can be as follows^[13]: The APC catheter was inserted through the biopsy orifice under endoscopic direct vision, about 3-5 mm from the lesion. The flow rate of argon jet was 0.8-1.2 L/min and the power

was 25-35 W. Coagulation treatment was performed every 1-3 s. The number of coagulations depended on the length of the lesion, the size of the local vascular network, the patient's tolerance, *etc.* The gas is sprayed along the blood vessel until the local tissue became white or burnt, the varicose veins disappeared, and the vascular network was blurred. Based on the LDRf classification as described by previous studies^[14,15], APC was first used in 2007 to treat EV with a diameter ≤ 0.3 cm^[13,16], and demonstrated high treatment safety. The aim of this review is to summarize these current research of APC in the treatment of EV and to discuss its clinical value and future development.

APC COMBINED WITH EVL TREATMENT

EVL achieves hemostasis through mechanically ligating varicose veins, which is one of the important ways to treat EV. The esophageal vein can be divided into four zones, gastric zone, palisade zone (PZ), perforating zone (Piz), and truncal zone. The principle of EVL in the treatment of EV is based on the esophageal venous drainage system, and it mainly ligates the PZ and Piz varicose veins to occlude and remove the submucosal veins in the PZ. Then, a thrombus was then formed, gradually blocking the deep and perforating veins^[18]. Pathological studies have shown that EVL treatment can maintain the integrity of the muscular layer and ischemic necrosis was found within 1-4 d after the ligation area. The formed mucosal ulcers gradually re-epithelialized and then formed scar tissue, which made the blood vessels disappear^[17,18]. It is believed that EVL can quickly eliminate varicose veins and the operation is simple^[19], so it is widely advocated. However, because EVL cannot damage deep veins and perforating veins, studies have shown that the recurrence rate of esophageal varices after EVL can reach 21.3%-92% and the rates of complications are about 2%-31%. Common complications include chest pain, esophageal ulcers, difficulty swallowing, esophageal stenosis, *etc.*^[18]. A previous study has used APC for sequential treatment after EVL for the first time and showed that APC combined with EVL was superior to simple EVL, representing an effective method to achieve complete eradication of EV^[14]. A number of randomized controlled trials have shown (Tables 1 and 2) that sequential treatment with EVC after EVL can significantly reduce the recurrence rate of varicose veins and the rates of re-bleeding and death compared with EVL treatment alone^[11,13,19-21]. The rate of postoperative fever was higher in the combined treatment group than in the EVL group alone. A meta-analysis showed that EVL combined with APC may be the best choice to reduce the rates of re-bleeding and mortality^[22]. At present, it is suggested to perform APC treatment after 1-3 wk of EVL operation recovery, that is, the two sequential methods are used to reduce the incidence of postoperative esophageal stenosis^[20]. The incidence of difficulty swallowing seems higher after EVL combined with APC treatment in most studies as shown in Table 2. The main adverse events included varicose veins, recurrent bleeding, fever, difficulty swallowing, esophageal stenosis, and mortality. Nakamura *et al*^[11] reported that esophageal stenosis occurred in only one patient. The eradication course of EVL combined with APC treatment showed an increasing trend compared with EVL alone due to the addition of APC^[11,20,21]. Harras *et al*^[20] believed that it is safe and effective to perform APC treatment at a distance of 5 cm from the cardia of distal esophagus. However, the sample size of the research is small and further research is required to confirm the findings.

APC COMBINED WITH EIS TREATMENT

Because EVL is simple, safe, and does not require sclerosing agents, it is often regarded as the first-line treatment for EV. In contrast, EIS is mostly a selective treatment^[3,23]. However, most studies have shown that the recurrence of varicose veins after EIS is lower than that after EVL^[24]. The recurrence rate is about 11%-24% and the re-bleeding rate after EIS is about 4%-20%^[20,25,26]. Deguchi *et al*^[3] conducted a retrospective study comparing sequential APC treatment (62 cases) after EIS with EIS alone (124 cases) and showed that the recurrence rates were 9.7% and 11.3% after 1 year and 2 years in the combined treatment group, respectively, while they were 29.0% and 34.7% in the treatment alone group. The Kaplan-Meier curve showed that the recurrence rate in the combination treatment group was significantly lower without serious adverse events related to APC. Another study by Kondo *et al*^[27] showed that EIS combined with APC for the treatment of EV does not seem to have much effect on

Table 1 Basic characteristics of patients in clinical studies of “argon plasma coagulation combined with endoscopic variceal ligation” vs “endoscopic variceal ligation alone” in treatment of esophageal varices

Ref.	Country	Sample size (EVL+APC/EVL)	Age (EVL+APC/EVL) (mean ± SD)	Gender (male/female)	Liver function classification (EVL+APC/EVL)	Pathogenic factors (EVL+APC/EVL)	Varicose vein types (EVL+APC/EVL)	Follow-up (EVL+APC/EVL) (mean ± SD)
Nakamura <i>et al</i> ^[11] , 2001	Japan	30/30	63.7 ± 5.8/60.8 ± 7.1	EVL+APC: 22/8; EVL: 21/9	A: 9/7; B: 17/18; C: 4/5	Virus: 25/26; Alcohol: 4/4; Others: 1/0	F2: 19/17; F3: 11/13	18.5 ± 6.8/15.8 ± 7.7
Cipolletta <i>et al</i> ^[20] , 2002	Italy	16/14	62.8 ± 5.5/60.8 ± 6.2	EVL+APC: 11/5; EVL: 10/4	Not mentioned	Not mentioned	F2: 10/9; F3: 6/5	16.2 ± 5.8/16.5 ± 5.1
Harras <i>et al</i> ^[20] , 2010	Egypt	50/50	50.64 ± 10.43/48.96 ± 10.27	Not mentioned	A: 10/14; B: 34/32; C: 6/4	Virus: 50/50; Alcohol: 0/0; Others: 0/0	F2: 3/0; F3: 47/50	16.3/17.4
Hamza I <i>et al</i> ^[21] , 2012	Egypt	30/30	50.23 ± 2.095/50 ± 2.104	EVL+APC: 16/14; EVL: 18/12	The two groups have the highest proportion of B grade, and there is no difference between the groups	Not mentioned	Post operative 3 mo: F0: 18/15; F1: 12/15; F2: 0/0	Follow-up 3 mo and 6 mo
Kamal <i>et al</i> ^[13] , 2017	Egypt	20/20	48.4/47.8	Not mentioned	A:12/12; B: 6/6; C: 2/2	Virus: 20/20; Alcohol: 0/0; Others: 0/0	Not mentioned	Not mentioned

According to the Japanese Society of Portal Hypertension, F0: No varicose veins; F1: Linear small varicose veins; F2: Beaded medium Varicose veins; F3: Nodular or large varicose veins. APC: Argon plasma coagulation; EVL: Endoscopic esophageal varices ligation.

Table 2 Clinical results of “argon plasma coagulation combined with endoscopic variceal ligation” vs “endoscopic variceal ligation alone” in treatment of esophageal varices

Group	Nakamura <i>et al</i> ^[11] , 2001		Cipolletta <i>et al</i> ^[19] , 2002		Harras <i>et al</i> ^[20] , 2010		Hamza I <i>et al</i> ^[21] , 2012		Kamal <i>et al</i> ^[13] , 2017	
	EVL+APC	EVL	EVL+APC	EVL	EVL+APC	EVL	EVL+APC	EVL	EVL+APC	EVL
Sample size	30	30	16	14	50	50	30	30	20	20
Varicose veins	No recurrence 74.2%	No recurrence 49.6%	Recurrence 0%	Recurrence 42.8%	Recurrence 4%	Recurrence 28%	Post operative 6 mo; F0: 16; F1: 14; F2: 0	Post operative 6 mo; F0: 10; F1: 19; F2: 1	Recurrence 21.1%	Recurrence 68.4%
Recurrent bleeding	3.3%	6.7%	0%	7.2%	2%	8%	0%	0%	0%	10.5%
Fever	63.3%	33.3%	81.3%	0%	34%	8%	6.7%	6.7%	60%	15%
Difficulty swallowing	30%	26.7%	50%	0%	36%	12%	3.3%	3.3%	35%	30%
Esophageal stenosis	3.3%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Mortality	0%	0%	0%	0%	8%	12%	0%	0%	5%	5%
Eradication course	2.9 ± 0.6	2.5 ± 0.6	Not mentioned	Not mentioned	4.6 ± 0.7	3.7 ± 0.5	4.43	4.23	Not mentioned	Not mentioned

According to the Japanese Society of Portal Hypertension, F0: No varicose veins; F1: Linear small varicose veins; F2: Beaded medium Varicose veins; F3: Nodular or large varicose veins. APC: Argon plasma coagulation; EVL: Endoscopic esophageal varices ligation.

the portal pressure gradient. Two studies have shown that^[3,28] sequential APC treatment after EIS is safe and can prevent the recurrence of esophageal varices. The above studies preliminarily suggest that combined APC treatment after EIS can reduce the recurrence rate without obvious adverse reactions. But its actual clinical value still needs further verification by large cohort clinical studies.

SIMPLE APC FOR EVS WITH A DIAMETER ≤ 0.3 CM

EVL and EIS are the most common methods for the endoscopic treatment of EV, but the two methods can only target varicose veins > 0.3 cm in diameter^[15]. However, 5% of cirrhotic patients without varicose veins develop EV after 1 year and 28% after 3 years; and 12% of patients with mild EV after 1 year and 31% after 3 years progress to severe EV^[16]. Therefore, early diagnosis and treatment are essential for preventing EV progression. A previous study reviewed seven patients with APC treatment for LeD0.3Rf0 classification, whose relapse time was 4 mo to 17 mo, and there were no serious complications^[14]. In addition, previous studies have also shown that APC can effectively seal blood vessels with a diameter of ≤ 0.3 cm, thereby alleviating the recurrence of varicose veins^[17]. The study preliminarily confirmed that APC is safe and effective for the treatment of varicose veins with a diameter of ≤ 0.3 cm, but prospective research with large samples are still needed.

PERSPECTIVES

APC has been widely used in recent years and the technology is still improving. The setting parameters of APC devices from different manufacturers are slightly different. Several reports used APC 300/ICC 200 (Erbe, Germany) with the setting of 50-60 W and the flow rate of 1.5-2.0 L/min^[19,29]. However, APC 2 (Erbe, Germany) is now very common on the market and provides parameter settings including output power, argon flow rate, and mode. The new generation, APC 3 (Erbe, Germany), replaces the output power with the effect, and the number of adjustable gears is increased to 100 gears, which is more refined. Different parameters have different effects. Specifically, the factors that affect APC treatment efficacy include output power, duration, current intensity, argon flow rate, and the distance between the probe and the tissue. In order to eradicate the lesion, domestic endoscopists currently use 25-30 W output power for the treatment^[13], while foreign endoscopists often use higher output power (50-60 W) to treat precancerous lesions of the digestive tract, such as Barrett's esophagus^[30]. However, higher power is easy to damage the muscular layer, resulting in esophageal stenosis. Therefore, hybrid-APC was developed (Erbe, Germany, Tübingen) in recent years. That is a novel multi-functional instrument, which integrates APC and needle-free submucosal injection, so as to reduce thermal damage of the muscle layer from ablation through creating a submucosal water cushion before APC ablation^[31]. So far, there has been no proof about the effect of difference of APC settings on EV and the treatment usually depends on the experience of endoscopists. Further studies about the application of different APC technology should be discussed, such as precise APC, pulse APC, and hybrid-APC.

CONCLUSION

Considering the current relevant research results, APC has considerable efficacy and safety in the treatment of EV. Its clinical application and characteristics can be summarized as follows: (1) APC can be used for ablation of varicose veins that meet Le D0.3 Rf0 classification with a good therapeutic effect, which can eradicate esophageal varicose veins very quickly and help to prolong the time to recurrence and expand the monitoring interval of endoscopic observation, thereby reducing the psychological burden of patients; (2) According to individual differences, patients with an EV diameter > 0.3 cm can choose EVL or EIS treatment, and postoperative combination therapy with APC is feasible to reduce the relapse rate; (3) Since the coagulation depth of APC is limited to 3 mm, perforation is not likely to occur and there are no obvious complications; and (4) APC is non-contact coagulation, so it will not cause adhesion and secondary bleeding caused by adhesion. However, the above conclusions still need to be verified by large cohort clinical studies.

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