

Chapter 25

Endoscopic Treatment of Esophageal Varices: Consolidation Method Following Ethanolamine Oleate-Aethoxysklerol Combination Therapy



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Abstract To further reduce the rate of recurrence following the eradication of esophageal varices with endoscopic injection sclerotherapy using ethanolamine oleate (EO)-aethoxysklerol (AS) combination method, we introduced the consolidation method (mucosal fibrosis method using AS, laser, or argon plasma coagulation (APC)). The consolidation method for esophageal varices consists essentially of complete disappearance of esophageal varices using the EO-AS combination method followed by fibrosing of the lower esophagus with AS, laser, or APC. APC consolidation has been widely performed to date due to its usability and efficacy in further preventing variceal recurrence. Although the whole lower esophagus is treated including thrombotic varices and normal esophageal mucosa, this method can make fibrosis all round in the esophageal wall without esophageal stenosis. APC has also been used to prevent recurrence after endoscopic variceal ligation and is reported to be effective.

Keywords Esophageal varices · Obara method (EO-AS combination method) APC consolidation method (mucosal fibrosis method using APC) · EVL-AS combination method and APC consolidation method

25.1 Introduction

In Japan, endoscopic injection sclerotherapy (EIS) in the form of the ethanolamine oleate (EO)-aethoxysklerol (AS) combination method (Obara method) was introduced by Obara et al. in 1987 [1] and has been widely performed as an effective therapy for the eradication and recurrence prevention of esophageal varices. However, although the EO-AS combination method has led to a reduction in the

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recurrence rate, a non-bleeding recurrence rate of 31.3% was reported 5 years after the complete eradication of esophageal varices. Nevertheless, among those cases treated using the EO-AS combination method, esophageal stricture was observed as a complication of AS injection in some cases where no recurrence had been found even 5 or 6 years after treatment, which suggested that recurrence might be prevented if recurrence-prone veins were thoroughly treated with AS.

In 1989, Obara et al. [2] introduced the AS consolidation method (mucosal fibrosis method using AS); however, of 42 cases treated using this method, 10 (23.8%) were associated with esophageal stricture, which required endoscopic balloon dilatation. Accordingly, in 1994, Obara et al. introduced the laser consolidation method (the mucosal fibrosis method using a laser) [3], under which the lower esophageal mucosa is irradiated with a laser circumferentially to form a circumferential ulcer and replace the breeding bed for esophageal varices with a mass of dense fibrous tissues without causing esophageal stricture. In 1994, Grund KE et al. [4] reported the first clinical experience of endoscopic argon plasma coagulation (APC) to upper and lower gastrointestinal tracts using special application probes developed by the authors, which fit into the working channel of standard endoscopes. Following this, APC consolidation (mucosal fibrosis using APC) began to be applied to obliterated esophageal varices and has been widely applied to date on account of its efficacy and ease of application.

This chapter describes the indications, procedures, and efficacy of the APC consolidation method.

25.2 APC Consolidation Therapy

25.2.1 Indications

Treatment with the APC consolidation method is indicated for bleeding cases, elective cases, and recurrent cases. For prophylactic cases, this method is indicated for endoscopic treatment-resistant cases, alcohol-related cirrhosis cases, and hepatocellular carcinoma-complicated cases with portal vein invasion (Vp) 0-2 [5, 6]. Moreover, the APC consolidation method is indicated for cases where the advanced development of periesophageal veins and the presence of large perforating veins are observed with an ultrasound miniprobe after the completion of EIS because such cases display a high potential for recurrence [7].

25.2.2 APC Consolidation Procedure Following the EO-AS Combination Therapy

In open surgery, laparoscopic surgery, and thoracoscopic surgery, APC has been used for the hemostasis of superficial and diffuse hemorrhages from parenchymatous organs and for the devitalization of various tissues. Moreover, in endoscopic treatment, the development of special probes, which can be applied through flexible

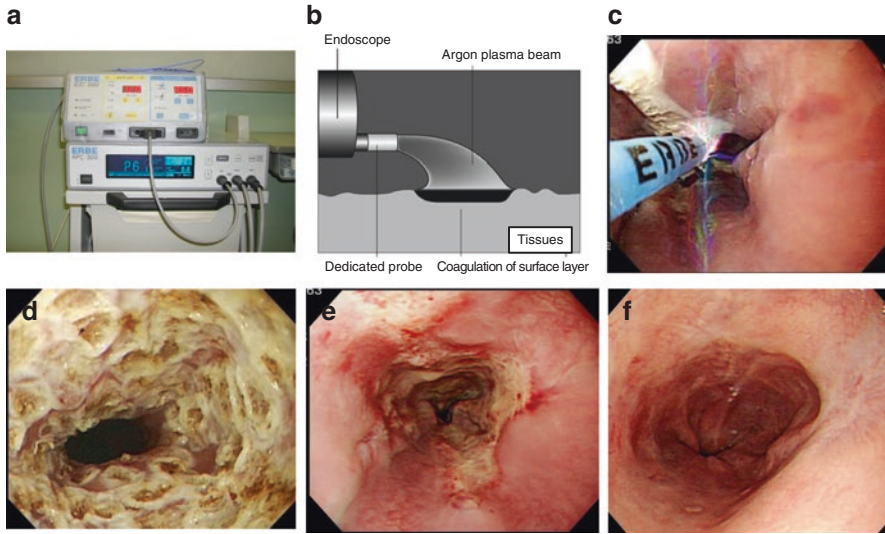


Fig. 25.1 APC consolidation procedure. (a) The APC system. (b, c) The argon gas emitted from the probe is blown onto the tissue, and the coagulating current is conducted through the gas like a spray to coagulate the tissue. The output power is 40 W, and the argon gas flow is 1 L/min. (d) The lower esophagus is cauterized circumferentially without leaving any space until it is covered with a shallow whitish ulcer. (e) Part of the shallow ulceration is still visible 1 week later. Additional treatment can be applied as required. (f) The ulcer appears scarred when observed 2 weeks later. *APC* argon plasma coagulation

endoscopes, has made it possible to utilize APC in endoscopic treatments of esophageal varices [4]. The APC system we use consists of an ERBE Erbotom ICC200 electrosurgical generator with an ERBE APC300 argon plasma coagulator and a dedicated disposable probe-emitting argon gas from its tip. The output power is 40 W, and the argon gas flow rate is 1 L/min. The argon gas emitted from the probe is blown onto the tissue, and the coagulating current is conducted through the gas like a spray to coagulate the tissue (Figs. 25.1 and 25.2).

When the esophageal varices, their feeding veins, and the surrounding small veins disappear as a result of the EIS using the EO-AS combination method, the APC consolidation can be applied. The lower esophageal mucosa is treated circumferentially by means of the APC technique to form a circumferential ulcer and to replace the mucosal and submucosal layers with a mass of dense fibrous tissues. The goal of this treatment is to prevent recurrence by hardening the breeding bed for the varices (Fig. 25.3) [8, 9].

25.3 Validation of Consolidation Methods Following the EO-AS Combination Therapy

Chronological changes in the 1st to 3rd layers of the esophageal wall were observed in 19 cases where EUS examination was performed before and after treatment with the EO-AS combination therapy followed by AS consolidation [2, 10]. The controls

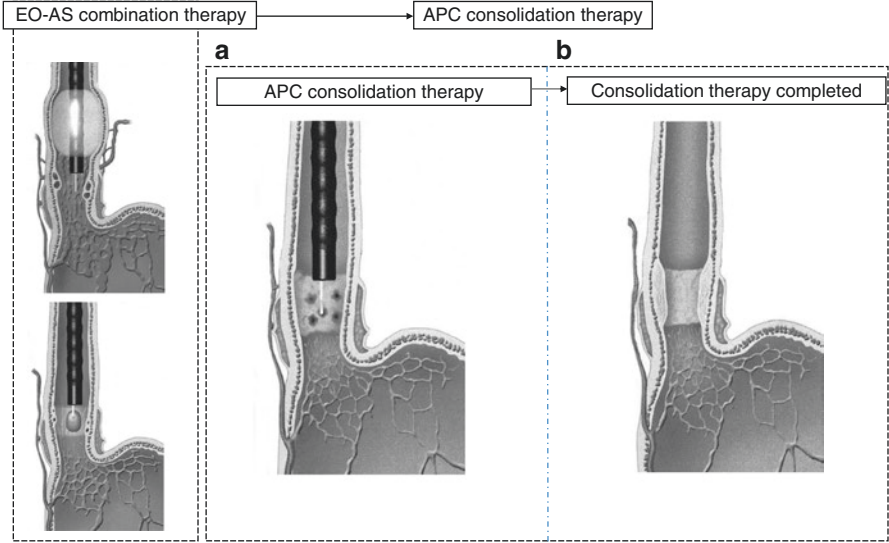


Fig. 25.2 EO-AS combination therapy followed by APC consolidation therapy. (a) Following EO-AS combination therapy, apply APC circumferentially on the lower esophagus to form a circumferential ulcer. (b) When the ulcer has healed, the esophageal wall will be replaced by thick fibrous tissues (sclerosis). *EO* ethanolamine oleate, *AS* aethoxysklerol, *APC* argon plasma coagulation

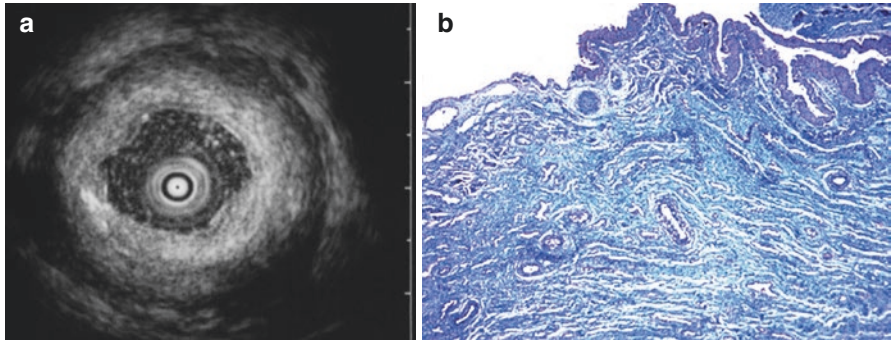


Fig. 25.3 EUS and histopathological findings after application of APC consolidation (autopsied case). (a) The esophageal mucosa and submucosa are amorphous and have thickened. No small blood veins can be seen in the wall. (b) The esophageal mucosa and submucosa have been replaced with dense fibrous tissues. No development of new blood veins is observed. Sclerosis of the esophageal wall has been made to eliminate the breeding ground for esophageal varices, preventing a recurrence. *EUS* endoscopic ultrasonography, *APC* argon plasma coagulation

were 19 patients with healthy esophagus (Table 25.1). In the EUS findings 1 week after consolidation therapy, 1st to 3rd layers (equivalent to mucosa-submucosa layers) were significantly thickened so that it was difficult to distinguish each layer, and ultrasound produced a low echoic parenchymal pattern. This was caused by

Table 25.1 Chronological EUS observation of the esophageal wall thickness after AS consolidation following EO-AS combination therapy

Period after treatment (<i>n</i> = 19)	1st–3rd layer (mucosa-submucosa)/mm (mean thickness/mm)	4th layer (muscle layer)/mm (mean thickness/mm)	1st–4th layer (mucosa-muscle layer) (mean thickness/mm)
1–3 (weeks)	3.0–9.0 (5.0)	0.6–3.1 (1.7)	5.0–10.0 (6.7)
6–12 (months)	3.0–3.5 (3.2)	0.5–2.2 (1.3)	4.0–5.0 (4.5)
14–19 (months)	2.0–4.0 (3.0)	0.8–2.0 (1.2)	3.0–6.0 (4.2)
Normal esophagus (<i>n</i> = 19)	0.9–1.3 (1.0)	0.5–1.0 (0.7)	1.4–2.0 (1.7)

EUS endoscopic ultrasonography, AS aethoxysklerol, EO ethanolamine oleate

inflammatory changes, which also generated a tentative sense of constriction. By approximately 1 month after the consolidation therapy, the inflammatory changes were completely replaced with fibrous tissues, following which high echoic EUS images of the 1st to 3rd layers were observed for a long period. Compared with a normal esophagus, the esophageal wall treated using the consolidation method remains thick for a long time, resulting in the effective prevention of esophageal variceal recurrence.

Obara et al. compared the thickness of the esophageal wall observed with EUS and the incidence of recurrence in 11 patients who received laser consolidation with those in 57 patients who received AS consolidation after EO-AS combination therapy [3]. The mean thickness of esophageal wall after consolidation was 6.3 mm in the laser group and 6.4 mm in the AS group. No recurrence was observed in the laser group (follow-up period of 3–17 months), while recurrence was observed in two (3.5%) patients in the AS group (follow-up period of 1–4 years). In addition, esophageal constriction was not observed in the laser group. These results showed that both laser and AS consolidation were equally effective in preventing variceal recurrence after EO-AS combination therapy and that laser consolidation was also free from esophageal constriction.

Kikuchi et al. [11] reported on chronological changes in the esophageal wall in 21 patients treated using the APC consolidation method and on pathological findings in 1 autopsied case. According to the report, the submucosa of the esophageal wall in particular remained thickened for more than 1 year after APC consolidation therapy. The cumulative recurrence rate after 2 years was 13.8%. Furthermore, pathological findings from the autopsied esophageal wall 2 weeks after APC consolidation therapy showed that inflammation occurred not only in the mucosa but also in the submucosa as well as partially in the muscularis propria, where it formed granulation tissue. Obara et al. [10] also reported that AS consolidation partially affected the muscularis propria because slight thickening of the 4th layer of the esophageal wall was observed, indicating effective recurrence prevention.

25.4 APC Irradiation Procedure Following EVL-AS Combination Therapy

As EIS using EO is contraindicated in patients with Child-Pugh grade C, TBIL 4 mg/dL, or more, EVL can be combined with EIS using AS in order to reduce the high rate of variceal recurrence after EVL. Using this EVL-AS combination method, rubber O-rings are placed densely onto the esophageal varices located between the esophagogastric junction and the lower esophagus. A week later, 1–2 mL of 1% AS per point is injected into the mucosa in the clearances made between the regions treated using EVL (Fig. 25.4).

Although the Obara consolidation method was originally applied using AS or a laser following EO-AS combination therapy where feeding veins are obliterated, the APC consolidation method following EVL was also introduced and performed to prevent rebleeding or recurrence within a short period [12]. APC consolidation after EVL-AS combination therapy is a procedure in which the normal lower esophageal mucosae located between the ulcers formed after EVL-AS combination therapy are cauterized using APC. This method has also been performed to date and can make it possible to avoid bleeding to death in cases with severe hepatic disorder or advanced HCC.

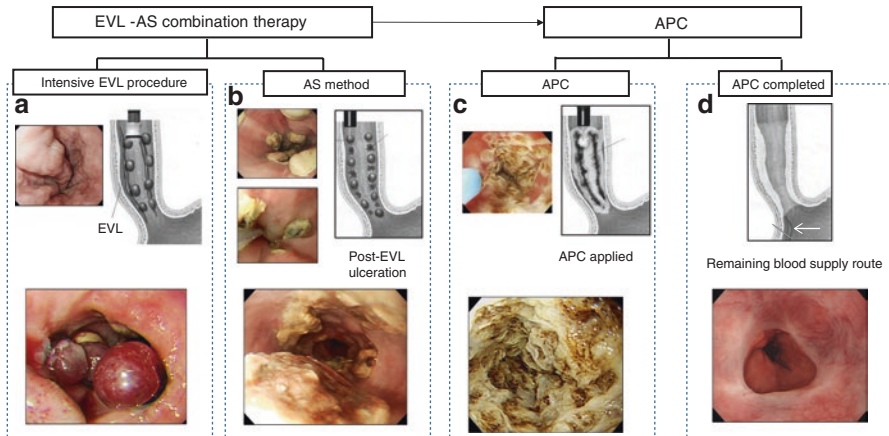


Fig. 25.4 EVL-AS combination therapy followed by APC. (a) A dense array of rubber O-rings are hooked onto the esophageal varices located from the esophagogastric junction to the lower esophagus. (b) AS is injected into the mucosa between ulcers formed after EVL so that the mucosa will bulge. (c) The remaining mucosa in the lower esophagus (except for the ulcers formed by the AS method) is cauterized circumferentially and uniformly with APC. (d) As the circumferential ulcers heal, the esophageal wall is replaced with thick fibrous tissue, but the blood supply route remains patent. *EVL* endoscopic variceal ligation, *AS* aethoxysklerol, *APC* argon plasma coagulation

25.5 Outcomes of Consolidation Therapy

Obara et al. [12] reported the outcomes and 5-year prognosis of employing various treatment regimes, namely, the EO-AS combination therapy alone, the EO-AS combination therapy with AS consolidation, the EO-AS combination therapy with laser consolidation, and the EVL-AS combination therapy with laser irradiation (Table 25.2). Compared with the EO-AS combination therapy alone, a greater number of treatment sessions were conducted using AS or laser consolidation. However, recurrence rates were significantly lower (in particular, the bleeding recurrence rate was 0%), and the recurrence-free period was typically longer in cases where AS or laser consolidation was additionally applied following EO-AS combination therapy.

Obara et al. [9] also found that the cumulative nonrecurrence rates after EO-AS combination therapy followed by laser consolidation were as high as 95.2% after

Table 25.2 Outcomes and prognosis after 5 years of employing four different treatment regimes

Treatment method	EIS (EO-AS combination therapy)	EO-AS combination therapy + AS consolidation	EO-AS combination therapy + laser consolidation	EVL-AS combination therapy + laser irradiation
No. of cases	86	70	63	24
Total no. of sessions for complete eradication (times)	4.2	9.1	9.2	7.6
Complication of esophageal stricture (%)	3.4	28.1	0	4.2
Esophageal wall thickness at completion of treatment with EUS (mm)	Irregular thickening 2.0–3.0	Circumferential thickening 6.4	Circumferential thickening 6.1	Irregular thickening 4.0–6.0
Non-bleeding recurrence rates (%)	31.4	7.1	7.9	37.5
Bleeding recurrence rates (%)	10.5	0	0	8.3
Recurrence-free period (months)	17.2	27.2	19.0	4.7

EO ethanolamine oleate, *AS* aethoxysklerol, *EIS* endoscopic injection sclerotherapy, *EVL* endoscopic variceal ligation, *EUS* endoscopic ultrasonography

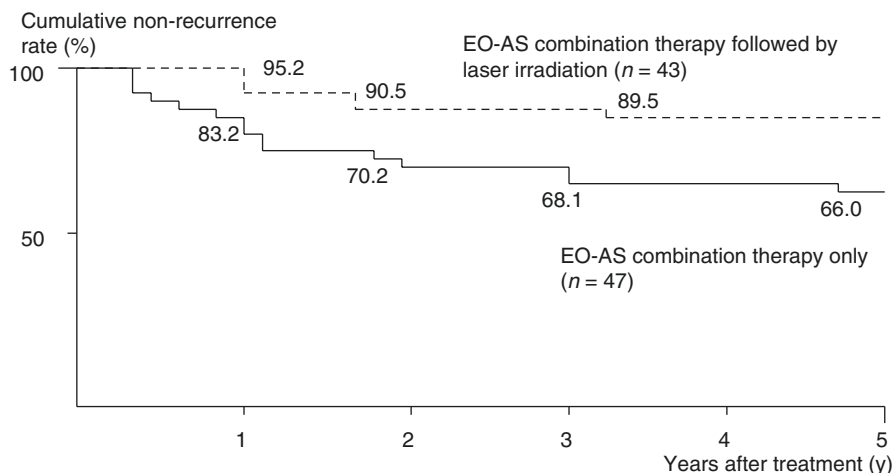


Fig. 25.5 Cumulative nonrecurrence rates in patients treated with the EO-AS combination therapy followed by laser consolidation in which esophageal varices were completely eliminated. *EO* ethanolamine oleate, *AS* aethoxysklerol

1 year, 90.5% after 3 years, and 89.5% after 5 years (Fig. 25.5). The recurrent cases were F0, RC-positive esophageal varices [13, 14] without bleeding and could be treated on an outpatient basis. By comparison, for cases treated using the EO-AS combination method alone, the rates were 83.2% after 1 year, 68.1% after 3 years, and 66.0% after 5 years. The recurrent cases were F1–F2, RC-positive esophageal varices, and bleeding was observed in about 10% of these cases. All the recurrent cases required inpatient treatment. Accordingly, the nonrecurrence rates were significantly higher in the cases treated using laser consolidation than in those treated with the EO-AS combination method alone.

Deguchi et al. [15] reported that cumulative recurrence rates in 124 patients treated using the EO-AS combination method alone were 29.0% after 1 year and 34.7% after 2 years, which were significantly higher than the 9.7% after 1 year and 11.3% after 2 years in 62 patients treated using the EO-AS combination method followed by APC consolidation. APC consolidation after the EO-AS combination therapy was found to be safe and significantly prevented the recurrence of esophageal varices. Harras et al. [16] divided 200 patients with bleeding esophageal varices into four groups and compared the recurrence rates of the four different regimes. Recurrence rates at 18 months after treatment were 2% in the scleroligation group, 4% in the EVL plus APC group, 14% in the EIS using EO group, and 28% in EVL-alone group, which indicated the efficacy of APC for recurrence prevention.

Matsui et al. [17] compared the efficacy of the consolidation therapy using APC with that using AS and reported that the accumulated nonrecurrence rates after 1 and 2 years were 93.3% and 84.0% in APC group and 87.9% and 76.9% in AS group, respectively. Both therapies were equally effective for preventing recurrence; however, esophageal constriction was observed in 8.8% of the AS group, and APC required fewer treatment sessions than AS consolidation.

25.6 Conclusion

Treatment of esophageal varices using EO-AS combination therapy followed by AS, laser, or APC consolidation has been shown to be safe for patients and effective in preventing further variceal recurrence. Although the efficacy of those three consolidation methods is comparable, APC consolidation is currently the most widely applied because AS consolidation generates esophageal stricture in some cases, and laser devices are expensive. In cases where EO is contraindicated but consolidation can be performed taking into consideration the patients' condition, APC consolidation following EVL-AS combination therapy is effective.

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