JGH Open An open access journal of gastroenterology and hepatology
Open Access
JGHF Journal of Gastroenterology and Hepatology Foundation
doi:10.1002/jgh3.12517

ORIGINAL ARTICLE

Clinical usefulness of combination therapy with polidocanol injection and argon plasma coagulation for gastric antral vascular ectasia

Hirosato Tamari,* Shiro Oka,† Shinji Tanaka,* Yuichi Hiyama,‡ Yuki Ninomiya,* Takahiro Kotachi,* Tomoyuki Boda,* Ryo Yuge,* Yuji Urabe,§ Yasuhiko Kitadai¶ and Kazuaki Chayama†

*Department of Endoscopy, †Department of Gastroenterology and Metabolism, ‡Department of Center for Integrated Medical Research, §Division of Regeneration and Medicine Center for Translational and Clinical Research, Hiroshima University Hospital and ¶Department of Health and Science, Prefectural University of Hiroshima, Hiroshima, Japan

Key words
argon plasma coagulation, gastric antral vascular ectasia, polidocanol injection.

Accepted for publication 19 February 2021.

Correspondence
*Shiro Oka, Department of Gastroenterology and Metabolism, Hiroshima University Hospital, 1-2-3, Kasumi, Minami-ku, Hiroshima 734-8551, Japan.

Email: oka4683@hiroshima-u.ac.jp

Declaration of conflict of interest: The authors declare no conflicts of interest in preparing this article.

Abstract

Background and Aim: Gastric antral vascular ectasia (GAVE) causes gastrointestinal bleeding. The initial treatment for GAVE bleeding is endoscopic hemostasis, and currently, the most performed technique to achieve hemostasis is argon plasma coagulation (APC). However, APC is associated with a high recurrence rate. To overcome this limitation, we examined the outcomes of the combination therapy of APC and polidocanol injection (PDI) for treating GAVE.

Methods: We retrospectively analyzed the outcomes of 15 consecutive GAVE patients treated with PDI + APC at Hiroshima University Hospital between November 2011 and September 2019 with respect to clinical characteristics, hemostatic efficacy, complications related to treatment, and recurrence rate.

Results: The mean age of patients (4 men and 11 women) was 74 ± 8.4 years. Patients had comorbidities of liver cirrhosis (seven patients, 47%), chronic renal failure (seven patients, 47%), and autoimmune diseases (seven patients, 47%). Endoscopic hemostasis with PDI + APC was performed in all patients (n = 15). The mean number of PDIs attempted to stop bleeding was 1.5 ± 0.8 (1–4), and the mean number of APCs attempted was 2.1 ± 1.2 (1–5). Complications related to treatment occurred in two patients (14%): ulceration in one patient and hematoma in another patient, both of whom were treated conservatively. Two patients (13%) had recurrences during the follow-up period (average period, 42 months). Both were cured with additional treatment of PDI only.

Conclusion: The combination therapy of PDI and APC is effective for GAVE with a low recurrence rate.

Introduction

Gastric antral vascular ectasia (GAVE) is responsible for 4% of nonvariceal upper gastrointestinal bleeding,[1] and it has been reported to occur in 3% of patients with type C cirrhosis.[2] Of patients with GAVE, 70% are women, and the average age at diagnosis is over 70 years.[2] Initial symptoms include black stools owing to bleeding and lightheadedness associated with anemia. Histological features include telangiectasia and hypertrophy in the mucosal lamina propria and submucosa, with mild inflammatory cell infiltration.[3–5] Underlying diseases include liver cirrhosis; chronic renal failure; and autoimmune diseases such as hyperthyroidism, hypothyroidism, scleroderma, hypertension, diabetes, etc. Although the cause of GAVE is unclear, there are various studies reporting autoimmunity, portal hypertension, and hormonal abnormalities as probable causes. The initial treatment for GAVE bleeding is endoscopic hemostasis, which includes argon plasma coagulation (APC),[6,7] laser procedure,[8] heat probes,[9] endoscopic band ligation,[10] and endoscopic submucosal dissection.[11] Currently, the most performed technique is APC for achieving hemostasis. This technique has a constant coagulation depth, low risk of perforation, and is relatively easy to perform even in cases of large lesions. However, the recurrence rate is high at 68.2%.[4] One possible reason for the high recurrence rate is that APC alone can only treat blood vessels within the mucosa and cannot treat the submucosal vessels. We have traditionally treated the submucosal vessels and intramucosal vessels with polidocanol injection (PDI) and APC, respectively, in patients with GAVE. Thus, we evaluated the outcomes of combination therapy of PDI and APC for treating GAVE.

Methods

Patients and methods. We retrospectively analyzed data from 15 consecutive patients with GAVE treated with PDI + APC at Hiroshima University Hospital between November 2011 and September 2019. Patients' backgrounds are presented in Table 1. As previously reported, patients were predominantly elderly women, with a high incidence of underlying liver disease, chronic renal failure, and autoimmune diseases. All patients presented to the outpatient clinic with symptoms of black stools and lightheadedness associated with acute hemorrhage and with anemia, respectively, on blood tests during routine follow-ups. Acute hemorrhage owing to GAVE was diagnosed in cases where emergency endoscopy revealed telangiectatic findings in the gastric antrum and body, with oozes and clots, or bleeding owing to flushing contacts. No patients had a previous history of GAVE treatment. Patients who were treated surgically or medically for bleeding owing to GAVE or who were in poor general condition and could not be followed up regularly using endoscopy were excluded. All patients provided informed consent before undergoing all procedures.

Procedures of PDI + APC therapy. A single-channel endoscope (GIF-Q260J, Olympus Optical Co, Ltd., Tokyo, Japan) was used. A vial of 1% polidocanol (10 mL), made in the dispensing room at Hiroshima University Hospital, was used rather than the one sold to the public. Polidocanol was filled in a 10-mL locking syringe and was injected into the gastric submucosa using a NeedleMaster (NM-600L-0423, Olympus, Tokyo, Japan) with a 23G disposable needle. Polidocanol (1 mL) was injected per puncture and was injected evenly into the areas of telangiectasia (Fig. 1). Additional cauterization with APC was performed using the FORCED APC mode of the Erbe VIO 300D and 200D generator modules (Erbe, Waldhoernlestrasse, Germany). The initial treatment was completed using only PDI. Three or 4 days after the first PDI, a second endoscopy was conducted with APC for the remaining bleeding area (Fig. 2). Thereafter, APCs were performed every 3 or 4 days until endoscopic hemostasis was achieved. If additional PDIs were needed, they were administered accordingly. We defined one treatment as a series of these procedures. Blood tests were performed after each endoscopic treatment to check hemoglobin (Hb) levels. After confirmation of endoscopic hemostasis and subsequent confirmation of endoscopic mucosal healing, blood tests (every 2 or 3 months) and annual endoscopy were performed. When bleeding and anemia progression owing to GAVE were observed, the patient was defined to have a recurrence of GAVE and was treated again with additional PDI + APC.

Table 1 Characteristics of the patients with gastric antral vascular ectasia

Variables	*n* = 15
Age, mean± SD, years	74 ± 8.4
Gender (male/female), *n*	4/11
Hb concentration, mean+SD, g/dL	6.5 ± 1.4
Red blood cell transfusion needs, *n* (%)	6 (40)
Comorbidities, *n* (%)	
Liver cirrhosis	7 (47)
Chronic renal failure	7 (47)
Diabetes	6 (40)
Hypertension	6 (40)
Hypothyroidism	5 (33)
Scleroderma	1 (7)
IgA nephropathy	1 (7)
Medication of antithrombic drug, *n* (%)	1 (7)

Evaluation. The primary outcomes of our study were the rate of cessation of bleeding and the recurrence rate. Complications and time to recurrence were investigated as secondary outcomes. The following clinical characteristics of enrolled patients were evaluated: age, gender, Hb concentration, need for red blood cell transfusion, comorbidities, and use of antithrombotic drugs. Red blood cells were transfused when Hb concentration was <7.0 mg/dL on blood tests. GAVE limited to the antral with red spots aggregated in linear stripes was defined as watermelon type, and the rest was defined as the diffuse type. Endoscopic atrophy was defined as no atrophy, closed type, or open type according to the Kimura-Takemoto classification.[12] For clinical response or treatment success, we defined endoscopically complete or near-complete disappearance of GAVE telangiectasia and stabilization of Hb levels. Recurrence was defined as the progression of anemia and black stools during follow-ups and endoscopically confirmed bleeding owing to GAVE. Quantitative data were presented as mean ± standard deviation or percentages. This study conformed to the principles of the sixth revision of the Declaration of Helsinki (2008), and the study protocol was approved by the institutional review board of the Hiroshima University Hospital, which also granted us permission to access patients' information on October 22, 2020 (No. E-2241). Because of the retrospective design, the need for patient consent was waived.

Results

GAVE status and background gastric mucosa of patients are presented in Table 2. The endoscopic findings of GAVE were diffuse type (10 patients, 67%) and watermelon type (5 patients, 33%). Portal hypertensive gastropathy was identified in four patients (27%). With respect to the background mucosa of the stomach, seven patients (47%) had open-type atrophy, three patients (20%) had closed-type atrophy, and five patients (33%) had no atrophy. During the initial observation, eight patients (53%) had oozing, and seven (47%) had hemorrhage induced by washing contacts. The results of GAVE treatment are presented in Table 3. The first treatment involved PDI followed by additional APC in 15 patients (100%), with a mean number of PDI and APC sessions of 1.5 ± 0.8 and 1.9 ± 1.3, respectively, and hemostasis was confirmed in all patients. Complications related to treatment occurred in two patients (14%): ulceration in one patient and hematoma in one patient, both of which were treated conservatively. Follow-ups were terminated for patients who died after treatment. The mean observation period was 54 ± 34 months (5–107 months). Two patients (13%) had recurrences: One recurred 36 months after hemostasis with PDI + APC treatment, and the other recurred 48 months after hemostasis (mean time to recurrence was 42 months). Both recurrences

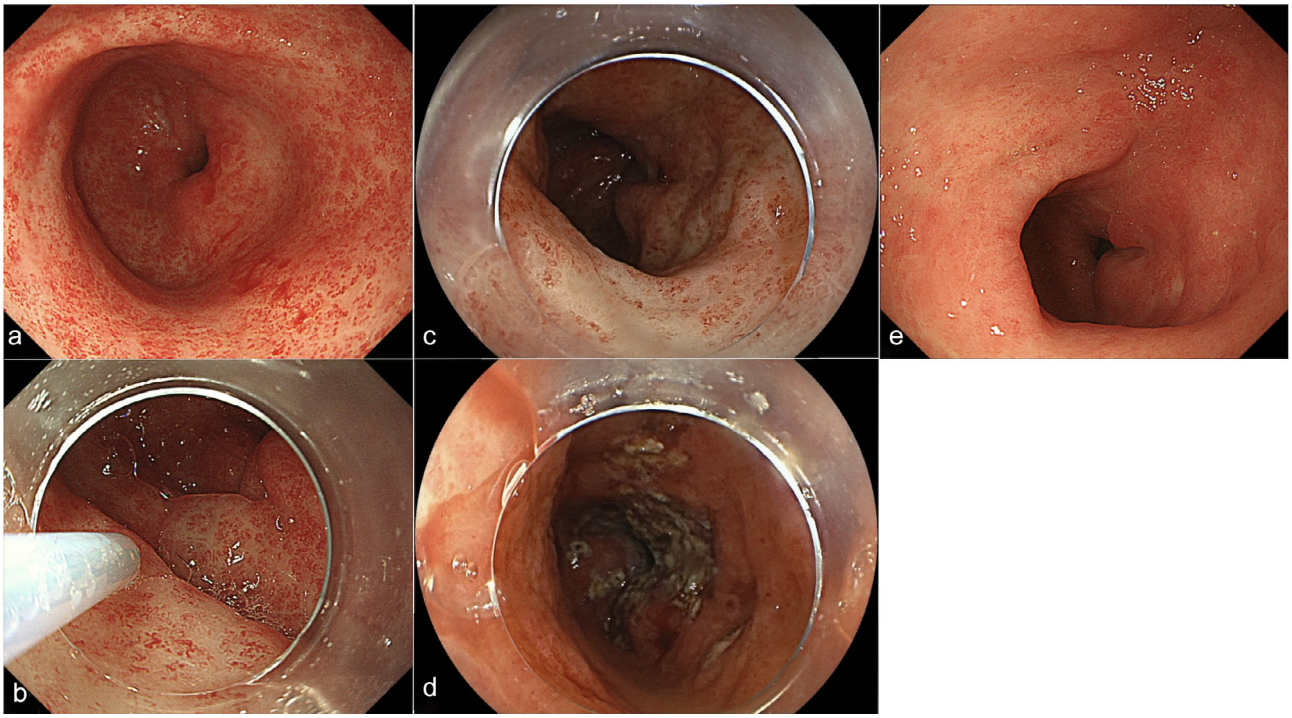

Figure 1 Changes in PDI + APC on GAVE. A 73-year-old woman with liver cirrhosis, liver cancer, and hypertension. (a) GAVE was found in the antrum, and microbleeding because of flushing was present. (b) Polidocanol was injected into the submucosa. (c) Avascular area was formed at the site of PDI. (d) APC was performed 3 days after the initial PDI. (e) Mucosal healing was observed 6 months after treatment. APC, argon plasma coagulation; GAVE, gastric antral vascular ectasia; PDI, polidocanol injection.

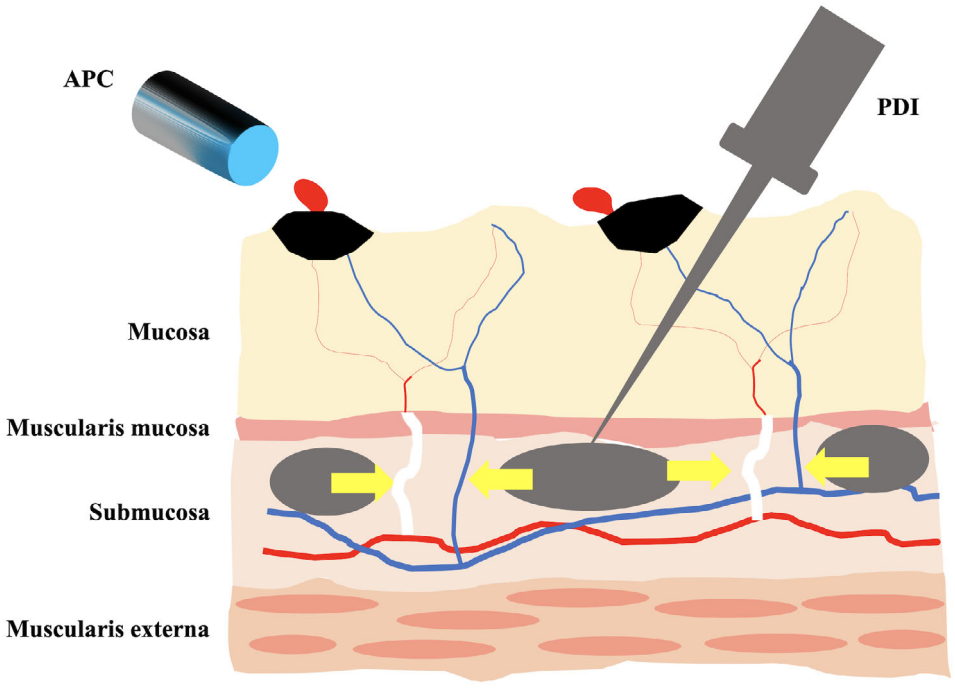

Figure 2 Schema of combination therapy with PDI and APC. Polidocanol injected into the submucosal layer had a hemostatic effect by pressuring the blood vessels in the submucosal layer, resulting in the formation of microthrombosis in the submucosal vessels. Vascular instrumentation reduced blood flow to the mucosa. Complete hemostasis could be achieved by performing APC for residual microbleeds. APC, argon plasma coagulation; PDI, polidocanol injection.

Table 2 Gastric antral vascular ectasia (GAVE) status and background stomach

Variables	*n* = 15
Type of GAVE, *n* (%)	
Diffuse	10 (67)
Watermelon	5 (33)
PHG (+), *n* (%)	4 (27)
Atrophic gastritis, *n* (%)	
Open type	7 (47)
Closed type	3 (20)
No atrophy	5 (33)
Intragastric bleeding during observation	
Oozing	8 (53)
No active bleeding	7 (47)

There are duplicates.
PHG, portal hypertensive gastropathy.

Table 3 Outcomes PDI + APC treatment for GAVE

Variables	*n* = 15
Cauterization	
Number of PDI session, mean ± SD	1.5 ± 0.8
Number of APC session, mean ± SD	2.1 ± 1.2
Observation period, mean ± SD, month	54 + 34
Cessation of bleeding, *n* (%)	15 (100)
Adverse events, *n* (%)	
Ulceration	1 (7)
Hematoma	1 (7)
Recurrence, *n* (%)	2 (13)
Time to recurrence, mean, month	42

There are duplicates.
APC, argon plasma coagulation; GAVE, gastric antral vascular ectasia; PDI, polidocanol injection.

were treated with only PDI, and hemostasis was achieved. No subsequent recurrence occurred. One death was observed during the observation period: The patient died of liver failure 5 months after treatment.

Discussion

This is the first report on the clinical usefulness of PDI + APC combination therapy for GAVE with a high hemostatic rate and low recurrence rate based on long-term prognosis.

APC,[6,7] laser treatment,[8] and heat probes[9] have been used for achieving endoscopic hemostasis in patients with GAVE. In various case series, APC has been shown to have >80% success for the treatment of GAVE.[4,13–15] For laser treatment, Gostout et al.[16] reported that, in 45 consecutive patients with GAVE, laser treatment resulted in a therapeutic response in over 80% of patients. For heat probes, it was reported that 8 of 10 patients responded to the treatment and had no recurrence during the follow-up period of approximately 21 months.[9] Among the various methods for treating GAVE, we used polidocanol, which has been used for treating upper gastrointestinal bleeding, such as esophageal varices. Polidocanol is a curing agent used for intravenous or intramucosal injection, and it has been shown to be effective for esophageal variceal bleeding, varicose veins of the lower extremities, and gastroduodenal ulcers.[17–19] We previously reported the usefulness of PDI for small-bowel angioectasia and hemangiomas, and there have been subsequent reports of PDI efficacy as well.[20–22] Okano et al.[23] reported the early and late hemostatic properties of PDI in dogs. The early hemostatic effects were because of pressure on the blood vessels and thrombosis formation in small blood vessels associated with interstitial edema. The late hemostatic effects were because of thrombus formation caused by vascular inflammation. Takeuchi et al.[24] also reported how PDI affected the gastric wall, especially the submucosal layer in dogs, and local injections of polidocanol had little effect on the arteries of the muscle layer, and no perforation was observed. APC is a noncontact, high-frequency coagulation method that combines argon plasma injection and high-frequency arc current discharge. It is often used for achieving hemostasis for acute nonvariceal upper gastrointestinal bleeding, chronic radiation proctopathy, and prevention consolidation therapy of esophageal varices.[14,25,26] Endoscopic hemostasis, especially APC, is the most common therapy for GAVE. However, the coagulation effect of APC is confined to the mucosal fascia and has only a slight spillover to the shallow submucosal layer; however, the risk of perforation is low and is considered safe.[27,28] APC is considered to have a high hemostatic effect but with a temporary effect.[29,30] In fact, the recurrence rate is high (35–78.9%),[15,31] and the cumulative rebleeding rates at 1, 2, and 3 years after the therapy were 50.3, 64.5, and 64.5%, respectively.[31] Fifteen recurrences occurred in an average of 7.7 months, and approximately 50% recurrence occurred in an average of 18 months.[18,32] Our combination therapy is thought to treat submucosal vessels with PDI and mucosal vessels with APC. GAVE is a condition in which dilatation and proliferation of blood vessels are observed not only in the mucosal layer but also in the submucosal layer. Only APC has a high recurrence rate because of its shallow coagulation depth, and it can only treat vessels in the mucosal layer.[33] Combination therapy with PDI + APC can be performed as vascular treatment of the mucosal layer with APC and submucosal treatment of the mucosa with PDI, enabling radical treatment of GAVE. It has been reported that polidocanol has an antiangiogenic effect in an in vitro study,[34] and it is possible that the inhibition of angiogenesis may prevent recurrence. Furthermore, a case report demonstrated that PDI was effective even in refractory cases that could not be cured using APC.[35] This suggests the possibility of a more complete treatment to compensate for the limitation of APC. Multiple sessions of APC treatment for GAVE are considered to be necessary.[36] The average number of additional APCs after PDI was 2.1 in our study. PDI is suggested to organize submucosal blood vessels, which reduces blood flow to the mucosal vessels and forms an avascular area in a short period. This may reduce the number of vessels that need to be hemostatic using APC and can also limit the damage to the gastric mucosa.

Our study has some limitations. First, this was a retrospective study with a small sample size in a single center. Second, the follow-up period was not long enough. We need to continue to follow up regularly using a surveillance program. Third, different endoscopists of varying skill levels performed the combination therapy of PDI + APC. Further accumulation of large-scale cases and a prospective multicenter study should be conducted.

In conclusion, the combination therapy of PDI + APC is effective as a therapeutic strategy for GAVE.

References

1 Dulai GS, Jensen DM, Kovacs TOG, Gralnek IM, Jutabha R. Endoscopic treatment outcomes in watermelon stomach patients with and without portal hypertension. *Endoscopy*. 2004; **36**: 68–72.
2 Fontana RJ, Sanyal AJ, Doherty MC *et al*. Portal hypertensive gastropathy in chronic hepatitis C patients with bridging fibrosis and compensated cirrhosis: results from the HALT-C trial. *Am. J. Gastroenterol.* 2006; **101**: 983–92.
3 Jabbari M, Cherry R, Lough JO, Daly DS, Kinnear DG, Goresky CA. Gastric antral vascular ectasia: the watermelon stomach. *Gastroenterology*. 1984; **87**: 1165–70.
4 Lee FI, Costello F, Flanagan N, Vasudev KS. Diffuse antral vascular ectasia. *Gastrointest. Endosc.* 1984; **30**: 87–90.
5 Probst A, Scheubel R, Wienbeck M. Treatment of watermelon stomach (GAVE syndrome) by means of endoscopic argon plasma coagulation. *Z. Gastroenterol.* 2001; **39**: 447–52.
6 Canard JM, Vedrenne B. Clinical application of argon plasma coagulation in gastrointestinal endoscopy. *Endoscopy*. 2001; **33**: 353–7.
7 Sou S, Nagahama T, Nomura H *et al*. Remarkable effectiveness of endoscopic argon plasma coagulation against diffuse antral vascular ectasia. *Dig. Endosc.* 2004; **16**: 166–8.
8 Bourke MJ, Hope RL, Boyd P *et al*. Endoscopic laser therapy for watermelon stomach. *J. Gastroenterol. Hepatol.* 1996; **11**: 832–4.
9 Petrini JL Jr, Johnston JH. Heat probe treatment for antral vascular ectasia. *Gastrointest. Endosc.* 1989; **35**: 324–8.
10 Eccles J, Falk V, Montano-Loza AJ *et al*. Long-term follow-up in patients with gastric antral vascular ectasia (GAVE) after treatment with endoscopic band ligation (EBL). *Endosc Int Open*. 2019; **12**: 1624–9.
11 Hashimoto S, Kobayashi M, Ajioka Y *et al*. A case of recurrent gastric vascular antral ectasia treated with endoscopic submucosal dissection [in Japanese]. *Gastroenterol Endosc*. 2010; **52**: 3259–66.
12 Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy*. 1969; **3**: 87–97.
13 Shashank G, Bilal A, Nicholas N. Endoscopic resolution and recurrence of gastric antral vascular ectasia after serial treatment with argon plasma coagulation. *World J Gastrointest Endosc*. 2017; **16**: 263–6.
14 Deguchi H, Kato J, Maeda Y *et al*. Argon plasma coagulation is effective for prevention of recurrent esophageal varices after endoscopic injection sclerotherapy: single-center case-control study. *Dig. Endosc.* 2016; **28**: 42–9.
15 Zepeda-Gómez S. Endoscopic treatment for gastric antral vascular ectasia: current options. *GE Port. J. Gastroenterol.* 2017; **24**: 176–82.
16 Gostout CJ, Viggiano TR, Ahlquist DA, Wang KK, Larson MV, Balm R. The clinica and endoscopic spectrum of the watermelon stomach. *J. Clin. Gastroenterol.* 1992; **15**: 256–63.
17 Romano G, Agrusa A, Amato G *et al*. Endoscopic sclerotherapy for hemostasis of acute esophageal variceal bleeding. *G. Chir.* 2014; **35**: 61–4.
18 Raetz J, Wilson M, Collins K. Varicose veins: diagnosis and treatment. *Am. Fam. Physician*. 2019; **99**: 682–8.
19 Asaki S. Efficacy of endoscopic pure ethanol injection method for gastrointestinal ulcer bleeding. *World J. Surg.* 2000; **24**: 294–8.
20 Igawa A, Oka S, Tanaka S *et al*. Major predictors and management of small-bowel angioectasia. *BMC Gastroenterol.* 2015; **15**: 108.
21 Igawa A, Oka S, Tanaka S, Kunihara S, Nakano M, Chayama K. Polidocanol injection therapy for small-bowel hemangioma by using double-baloon endoscopy. *Gastrointest. Endosc.* 2016; **84**: 163–7.
22 Aoyama T, Fukumoto A, Shigita K, Asayama N, Mukai S, Nagata S. Successful endoscopic sclerotherapy using polidocanol for small bowel hemangioma. *Intern. Med.* 2020; **59**: 1727–30.
23 Okano H, Nishida H, Imamura M *et al*. Endoscopic local injection of aethoxysklerol to upper gastrointestinal bleeding. *Gastroenterol Endosc*. 1986; **28**: 1233–6.
24 Takeuchi T, Narimiya N, Joki M *et al*. Experimental study on the effects of local injection of aethoxysklerol for gastric mucosa with special reference to the submucosal arterial plexus [in Japanese]. *Gastroenterol Endosc*. 1991; **33**: 695–704.
25 Havanond C, Havanond P. Argon plasma coagulation therapy for acute non-variceal upper gastrointestinal bleeding. *Cochrane Database Syst. Rev.* 2005; **2**: CD003791.
26 Peng Y, Wang H, Feng J *et al*. Efficacy and safety of argon plasma coagulation for hemorrhagic chronic radiation proctopathy: A Systematic Review. *Gastroenterol. Res. Pract.* 2018; **3087603**: 2018.
27 Farin G, Grund KE. Technology of argon plasma coagulation with particular regard to endoscopic applications. *Endosc. Surg. Allied Technol.* 1994; **2**: 71–7.
28 Canard JM, Vedrenne B. Clinical application of argon plasma coagulation in gastrointestinal endoscopy: has the time come to replace the laser? *Endoscopy*. 2001; **33**: 353–7.
29 Sebastian S, Mcloughlin R, Qasim A *et al*. Endoscopic argon plasma coagulation for the treatment of gastric antral vascular ectasia (watermelon stomach): long-term results. *Dig. Liver Dis.* 2004; **36**: 212–17.
30 Roman S, Saurin JC, Dumortier J, Perreira A, Bernard G, Ponchon T. Tolerance and efficacy of argon plasma coagulation for controlling bleeding in patients with typical and atypical manifestations of watermelon stomach. *Endoscopy*. 2003; **35**: 1024–8.
31 Nakamura S, Mitsunaga A, Oi I *et al*. Long-term follow up of gastric antral vascular ectasia treated by argon plasma coagulation. *Dig. Endosc.* 2006; **18**: 128–33.
32 Fuccio L, Zagari RM, Serrani M *et al*. Endoscopic argon plasma coagulation for the treatment of gastric antral vascular ectasia-related bleeding in patients with liver cirrhosis. *Digestion*. 2009; **79**: 143–50.
33 Chiu YC, Lu LS, Wu KL *et al*. Comparison of argon plasma coagulation in management of upper gastrointestinal angiodysplasia and gastric antral vascular ectasia hemorrhage. *BMC Gastroenterol.* 2012; **12**: 67.
34 Doganci S, Yildirim V, Erol G *et al*. Polidocanol (Lauromacrogol 400) has anti-angiogenic effects *in vitro* and *in vivo*. *Eur. Rev. Med. Pharmacol. Sci.* 2016; **20**: 1384–9.
35 Zulli C, Prete AD, Romano M *et al*. Refractory gastric antral vascular ectasia: a new endoscopic approach. *Eur. Rev. Med. Pharmacol. Sci.* 2015; **19**: 4119–22.
36 Herrera S, Bordas JM, Llach J *et al*. The beneficial effects of argon plasma coagulation in the management of different types of gastric vascular ectasia lesions in patients admitted for GI hemorrhage. *Gastrointest. Endosc.* 2008; **68**: 440–6.