Insights into the management of gastric antral vascular ectasia (watermelon stomach)

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Abstract: Gastric antral vascular ectasia (GAVE) is an uncommon but important cause of chronic gastrointestinal bleeding. It is often associated with systemic diseases such as autoimmune diseases, liver cirrhosis, chronic renal insufficiency and cardiovascular disease. The etiology of GAVE has not been fully explored and remains controversial. Diagnosis is mainly based on endoscopic presentation with flat or raised erythematous stripes radiating from the pylorus to the antrum and resembles a watermelon. Clinical presentation may range from iron-deficiency anemia secondary to occult blood loss, melena to hematemesis. In past decades, many therapeutic modalities including medical, endoscopic and surgical intervention have been introduced for GAVE treatment with variable efficacy. Herein, we review the efficacy and safety of these treatment options for GAVE.

Keywords: antrectomy, endoscopic hemostasis, gastric antral vascular ectasia, gastrointestinal bleeding

Received: 26 June 2017; revised manuscript accepted: 30 October 2017.

Introduction

Gastric antral vascular ectasia (GAVE), known as watermelon stomach, is characterized endoscopically by parallel red stripes, angiomatous lesions at antral mucosal folds resembling watermelon stripes.^{1,2} The diagnosis is usually established by specific endoscopic appearance. For uncertain cases, biopsy will offer histological clues with dilated tortuous mucosal capillaries, focal thrombosis, spindle cell proliferation and fibrohyalinosis.^{3,4}

It is a rare acquired vascular disease, responsible for around 4% of nonvariceal upper gastrointestinal bleeding and may cause chronic blood loss with iron-deficiency anemia.^{5–7} Clinical presentations differ widely, from asymptomatic occult blood loss to overt gastrointestinal bleeding. Most of these patients are elderly and females number roughly twice that of males. In addition, 60–70% of patients need blood transfusion due to recurrent anemia despite iron supplements. The etiology of GAVE is still unknown. However, certain comorbidities may exist including autoimmune disease (e.g. systemic sclerosis), liver cirrhosis, chronic renal failure, and cardiovascular disease.^{5,6,8,9} Several mechanisms have been suspected for the development of GAVE. Altered antrum motility and dysfunction inducing chronic mucosa trauma and subsequent submucosa fibromuscular hyperplasia and dilation of mucosal capillary are the main contributing factors.^{3,10}

Management of GAVE-related gastrointestinal bleeding is a clinically challenging issue. In the last two decades, many therapeutic options and modalities have been applied for GAVE. The purpose of this paper is to review these therapeutic options including medical, endoscopic and surgical management for GAVE (Figure 1).

Medical management

Variant medical treatments have been used to control GAVE bleeding; however, most of them were limited to case series and long-term

Ther Adv Gastroenterol

2018, Vol. 11: 1-9 DOI: 10.1177/ 1756283X1774747471

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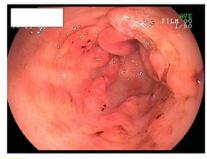
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Gastric Antral Vascular Ectasia (Watermelon stomach)



Endoscopic Management

Cryotherapy Nd:YAG laser Argon Plasma coagulation Endoscopic Band ligation Radiofrequency Ablation

Medical Management Corticosteroid Estrogen-progesterone Octreotide Tranexamic acid Thalidomide Surgical Management Antrectomy

Figure 1. Management of gastric antral vascular ectasia. Nd: YAG, neodymium-yttrium-aluminum garnet laser.

effectiveness and safety are the major considerations for medical treatment.

Corticosteroid is a familiar medication for autoimmune disease. It may involve the augmentation of vascular sensitivity and improvement of integrity of vascular endothelium. A case report has described the complete resolution of GAVE in systemic sclerosis treated with pulse intravenous steroid and cyclophosphamide.¹¹ There were also several case reports demonstrating that oral prednisolone improved blood loss and decreased blood transfusion requests in GAVE cases.¹²⁻¹⁴ However, long-term toxicity such as hyperglycemia, fluid retention and an immunocompromising effect has limited its clinical usage.

Hormone supply (estrogen–progesterone) has been used for postmenopausal women and has also been reported as successfully controlling recurrent gastrointestinal angiodysplasia bleeding and GAVE bleeding, maintaining hemoglobin concentrations in a case-series study.^{15–17} However, it did not modify the endoscopic appearance of GAVE and bleeding tended to recur at hormone treatment cessation.^{17,18} Long-term complications with gynecomastia and menorrhagia also present important clinical issues.

Octreotide, a long-acting somatostatin analogue, has many biological effects that indicate efficacy

in bleeding of gastrointestinal vascular abnormalities. Nardone and colleagues reported 17 case series with gastrointestinal tract vascular abnormality bleeding and of those 3 cases were cirrhosis with watermelon stomach. Octreotide treatment achieved clinical response with halted bleeding or reduction in blood transfusion.¹⁹ However, another study showed disappointing results in a noncirrhotic patient with GAVE.²⁰

Tranexamic acid, an antifibrinolytic agent, is widely used in clinical situations for traumatic or nontraumatic bleeding. Cases reports have shown its efficacy in reducing blood loss and transfusion requests in GAVE cases.^{21–23} However, the physician should be alerted to occasional severe complications such as central venous stasis retinopathy or pulmonary embolism in long-term treatment.

Thalidomide, an agent of angiogenesis inhibition, has been proven effective for treatment of gastrointestinal angiodysplasia bleeding.²⁴ Small cases reports showed its efficiency in endoscopic refractory angiodysplasia-related gastrointestinal bleeding. It has also been reported in the successful salvage treatment for argon plasma coagulation (APC) refractory GAVE for cirrhotic patients.^{25,26} However, until now, most of these have been small case reports and more studies are required to evaluate the efficacy and safety in GAVE treatment.

Endoscopic management

Cryotherapy

Cryotherapy is an endoscopic technique using nitrous oxide to apply an extremely cold temperature on affected tissue and achieve hemostasis by thermal destruction or necrosis of the mucosa. Limited data of cryotherapy on GAVE are available and, as far as we know, there are only two studies evaluating cryotherapy on the management of GAVE. The pilot study was presented by Kantsevoy and colleagues²⁷, and endoscopic cryotherapy was applied on 26 patients with mucosal vascular lesions of the gastrointestinal tract, including 7 patients with GAVE, who had a poor response to previous endoscopic therapy, including laser, thermal and electrosurgical coagulation, and had active bleeding. A total of five of the seven (71%) patients achieved cessation of bleeding after an average 3.6 sessions of cryotherapy and no recurrent bleeding or major complications were found during the 6-month follow-up period.27 The other study (in 2008) evaluated the efficacy of cryotherapy on 12 patients with GAVE, including 8 patients who had failed prior APC therapy. This study demonstrated that cryotherapy achieved a 50% complete response, defined as a significant improvement in endoscopic appearance associated with raising the hemoglobin level and no requirement for blood transfusion, and a 50% partial response, defined as incomplete ablation of GAVE on endoscopic assessment, with a stable hemoglobin level and reduced transfusions. In addition, there were no immediate or major complications after cryotherapy. It also found the mean hemoglobin level increased from 9.9 g/dl to 11.3 g/dl after cryotherapy, and large area lesions of GAVE, >70%, could be treated in an average 5-min treatment session.²⁸

Neodymium-yttrium-aluminum garnet laser coagulation

Neodymium-yttrium-aluminum garnet (Nd: YAG) laser, a thermal device, causes tissue destruction by absorption of laser light without direct contact. It makes extensive mucosal injury, up to 4–6 mm and achieves coagulation of superficial and submucosal vessels.²⁹ In the past, the Nd: YAG laser was widely used to treat gastrointestinal vascular ectasias and many case series reported >150 cases receiving Nd: YAG lasers for GAVE. In most case series, the Nd: YAG laser was effective both in stopping bleeding and decreasing the requirement for blood transfusions

after 1–4 sessions of laser therapy.^{5,6,8,9,30–32} The most recent study presented in 2004 retrospectively analyzed 24 transfusion-dependent patients who were treated with Nd: YAG for GAVE over an 18-year period. After a median of two treatment sessions and a follow-up median of 55 months, 20 of 24 patients (83%) had resolution of bleeding and remained transfusion-free for a median of 16 months.33 However, most studies were retrospective case series with a small number of patients and there were no randomized control trials available for evaluating Nd: YAG lasers with other endoscopic modalities, all of which suggested insufficient evidence of the efficacy of Nd: YAG lasers for GAVE. Nd: YAG lasers have been largely replaced by other treatment modalities because of higher cost and serious complications. The reported severe complications included perforation, antral narrowing, and mortality.8,33 The development of hyperplastic polyps and multiple focal gastric neoplasia has also been reported after repeated laser therapies.31,34

Argon plasma coagulation

APC is the other thermoablative method used as endoscopic therapy for GAVE. By using ionized argon gas (plasma) as a medium, APC produces high frequency electrical current flows to achieve tissue coagulation. APC is a noncontact thermal method and provides limited depth of mucosal injury, which reduces the risk of perforation.²⁹ Comparing APC with Nd: YAG lasers, both methods allow for the treatment of large areas, but there are several advantages of APC in the treatment of GAVE (Figure 2). Overall, APC is easier for endoscopists to use, safer due to its favorable side-effect profile, and less expensive.35,36 Even though there is no available randomized control trial to compare Nd: YAG lasers and APC, currently, APC has been the treatment of choice and the most widely used in the treatment of GAVE. Many studies have demonstrated the efficacy of APC, including a mean increase in hemoglobin levels and a decreased need for blood transfusions.³⁷⁻⁴¹ If bleeding recurs, APC was also useful to stop rebleeding.

Notably, however, most studies were case series with small numbers of patients and several sessions of treatment were almost always required to achieve hemostasis. Studies investigating the longterm efficacy of APC for GAVE demonstrated

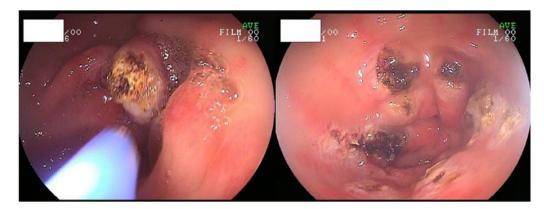


Figure 2. Argon plasma coagulation treatment of gastric antral vascular ectasia.

unsatisfactory results and high recurrence rates of GAVE bleeding after APC treatment were reported.42-44 Chiu and colleagues had compared APC in the management of upper gastrointestinal angiodysplasia and GAVE. Patients with GAVE cases had a higher recurrence rate of 78.9% versus 7.4% in simple angiodysplasia.45 A study investigated 20 GAVE patients in whom GAVE eradication was achieved by a median of three sessions of APC and prospectively followed for a mean period of 28 months. Fuccio and colleagues showed that relapse of GAVE was found in 15% patients after a mean of 7.7 months.43 The other large case series enrolled 62 gastric vascular ectasia patients, including 31 GAVE patients, and followed these patients for a mean of 47 months. Boltin and colleagues demonstrated that only APC achieved successful treatment but in only 25.8% of patients, which was defined as absence of further gastrointestinal bleeding, coupled with a 30% increase in the hemoglobin level on follow up, and most patients did not experience long-term resolution of upper gastrointestinal bleeding and anemia.44 The recurrent bleeding following APC may be related to its limited depth of mucosal coagulation and GAVE usually involves deeper structures, including the submucosa, which could not be treated adequately by APC.46

Although APC presumably has a favorable sideeffect profile due to its noncontact method and limited depth of mucosal injury, some major complications are still reported. Gastric outlet obstruction and hyperplastic polyps were reported as serious adverse events after APC treatment.^{43,47,48} Furthermore, Fuccio and colleagues also found hyperplastic polyps caused active bleeding in two of three patients who had hyperplastic polyps.⁴³

Endoscopic band ligation

Endoscopic band ligation (EBL) is initially designed for esophageal varices eradication. It has also been applied in the hemostasis for angiodysplasia, Dieulafoy's lesion and Mallory-Weiss syndrome.49,50 The first case using EBL as salvage treatment for GAVE was reported in 2006. After two sessions of EBL with a Multi-Band Ligator, hemoglobin became stable and serum ferritin normalized in 16 months of follow up.⁵¹ A subsequent retrospective study compared the efficacy of EBL with endoscopic thermal therapy for GAVE. It showed EBL had higher rates of bleeding cessation (67% versus 23%) and fewer treatment sessions (1.9 versus 4.7).52 Another two retrospective studies showed similar results with EBL superior to APC.^{53,54} In 2005, a prospective study enrolled 21 patients with GAVE who were treated with EBL. Clinical response was achieved in 19 patients (91%). Significant improvements in hemoglobin level and decreased blood transfusion were noted without serious complications.⁵⁵

Radiofrequency ablation

The principles and rationales of radiofrequency ablation (RFA) is to apply high-energy coaptive coagulation (power density of 40 W/cm²) to destroy the superficial mucosal capillary ectasia with the subsequent regeneration of epithelium composed of a normal capillary structure. The advantages of RFA include broader coverage of the mucosa surface and the uniform distribution of energy.⁵⁶ One pilot prospective study of RFA using the HALO90 ablation system as a GAVE treatment was published in 2008. A total of six patients were included and five patients were no longer dependent on blood

transfusions, increasing hemoglobin levels after a median of 1.6 RFA treatment sessions.⁵⁷ The two other larger studies included 21 and 24 patients, many of whom were refractory to APC and were transfusion-dependent. A clinical success rate of 80% (36/45), with increased hemoglobin levels and without further transfusions was achieved after a median of two treatment sessions. Only 1 out of 45 patients was reported to have complications of ulcer bleeding after RFA.58,59 The latest published study in 2017 included 15 patients, all of whom were refractory to APC. The clinical success with increasing hemoglobin levels and without further transfusions achieved an 80% rate after a median of two treatment sessions, and no procedure-related complications were reported.60

The definition of clinical success in the documented literature is "a transfusion-free condition without breakthrough gastrointestinal bleeding". However, whether the RFA was able to achieve endoscopic success, meaning the disappearance of watermelon mucosa, and histological success, meaning the normal microvascular structure in the regenerated epithelium, was still not evaluated. In other words, the current evidence indicates that RFA management achieves hemostasis and results in a transfusion-free condition but the mucosal capillary ectasia may not be completely eradicated. Also, GAVE can be divided into striped-pattern and diffused-pattern based on endoscopic appearance. Whether both subtypes respond equally well to RFA is not known and remains unstudied.

At present, the data regarding RFA efficacy are promising but only limited to case series. There are no randomized controlled studies comparing the clinical success rates and complications of different treatment modalities such as band ligation, APC and RFA. Owing to the rarity of GAVE, such double-blinded and head-to-head comparison studies are difficult to conduct. Consequently, based on the current evidence, RFA yields a satisfying clinical success rate without subsequent blood transfusions. The minimal time interval of 6 weeks between each treatment session is recommended and proton pump inhibitors should be prescribed.⁶¹ RFA is a well-tolerated and feasible method for patients with GAVE with poor response to APC and band ligation.

Surgical treatments

With the advances of endoscopic techniques, surgery is now reserved as the last resort for those patients with extensive severity in whom medical and endoscopic treatments fail. Antrectomies including Billroth I, II, and Roux-en-Y reconstructions were reported as being performed in the majority of patients (89%, 40/45).62 Other surgical approaches such as partial gastrectomy, total gastrectomy and esophagogastrectomy were also reported in some case reports.14 A laparoscopic approach with the advantage of minimal invasiveness instead of conventional open gastrectomy was reported.63 This yields shorter hospitalization times and also better functional recovery. The results of surgical hemostasis were satisfying. Of the 45 patients treated with a surgical procedure, all of them were transfusiondependent before treatment and no transfusion requirement was reported in each patient during the follow-up period of 1-48 months.⁶² The 30-day mortality rate after operation was 6.6% (3/45) and the causes of mortality were multiple organ failures instead of gastrointestinal bleeding.⁶⁴ The postoperative complications are similar to other benign etiologies for gastric resection. Late dumping syndromes developed at a 2.4% rate and no continual diarrhea case was ever reported in a 20-year follow up.65 Nutrition deficiencies such as vitamin D, vitamin B12 and iron are concerning and consequently, dietary counseling should be carefully given to improve nutritional outcomes.

Summary

Although GAVE is uncommon in clinical practice, it is frequently characterized with chronic gastrointestinal bleeding and transfusion requests tormenting both patients and physicians. In past decades, multiple treatment modalities have been used for bleeding control (Figure 1). Overall, medical treatment does not alter the endoscopic/ histologic figures of GAVE and has no definite role in the cure of GAVE-related bleeding. Small case-series reports have shown variable improvement of gastrointestinal blood loss but often patients drop out because of medication sideeffects. In recent years, endoscopic therapy has become the mainstay of GAVE management with acceptable success rates and few complications (Table 1). Nd: YAG lasers, APC, and RFA are

Method	Bleeding cessation rate ^a	Mean number of sessions	Complications ^b
Cryotherapy	50-71%	2-6	Major: ~0%; minor: 0-8%
Nd: YAG laser	60–100%	1–5	Major: 0–13%; minor: ~0%
Argon plasma coagulation	30-100%	2-6	Major: ~0%; minor: ~0%
Endoscopic band ligation	65–95%	2–3	Major: ~0%; minor: 8–12%
Radiofrequency ablation	67-86%	2–3	Major: ~0%; minor: 1–2%

Table 1. Endoscopic treatment for gastric antral vascular ectasia.

^aDefinition of bleeding cessation: rising hemoglobin level and no requirement for blood transfusion. ^bMajor complication: death, perforation, stenosis; minor complication: gastrointestinal upset. Nd: YAG, neodymium-yttrium-aluminum garnet.

based on thermal therapy to eradicate antral vascular ectasia. EBL is a mechanical method to obliterate the submucosal vascular plexus. These modalities have shown different numbers of treatment sessions and success rates in the management of GAVE bleeding. However, most of these studies had small numbers of patients, and as retrospective studies, might provide insufficient evidence to compare each method. Despite surgical antrectomy being more invasive and having higher complications than endoscopic therapy, it is the only method to achieve a complete cure for GAVE. Hence, we should weigh the pros and cons in different treatment modalities when it comes to refractory cases.

Funding

This work was supported by grants from the Kaohsiung Medical University Hospital, Taiwan (KMUH102-2M02).

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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