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Nitrous oxide cryotherapy ablation for refractory gastric antral vascular ectasia

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Abstract

Background: Argon plasma coagulation (APC) is typically the first-line therapy for gastric antral vascular ectasia (GAVE). However, many patients are refractory to APC ablation.

Objective: We examined the safety and efficacy of nitrous oxide CryoBalloon cryotherapy ablation for GAVE refractory to APC.

Methods: This is a retrospective review of patients with refractory GAVE treated with the CryoBalloon system. Technical success was defined as successful ablation of the visualized GAVE. Clinical success was defined by transfusion independence and percentage of GAVE that was eradicated.

Results: Twenty-three patients with GAVE were included, of whom 16 patients (70%) had two treatments with the CryoBalloon and seven patients (30%) had one treatment. Technical success was achieved in all patients. At six months, 19/23 (83%) were transfusion independent, while 20/23 (87%) had more than 75% of the GAVE eradicated. Patients were transfused an average of 1.8 units/month one year prior to cryotherapy and an average of 0.3 units/month up to six months post-cryotherapy ($p < 0.001$). The average increase in mean hemoglobin at six months was 2.55 g/dl. No acute or late adverse events were reported.

Conclusions: CryoBalloon ablation is an efficacious and safe modality for the treatment of GAVE. Prospective studies need to be conducted to determine comparative results to standard therapies.

Keywords

Ablation, watermelon stomach, gastrointestinal bleeding, cryotherapy

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Key points

- Argon plasma coagulation (APC) is typically first-line therapy for gastric antral vascular ectasia (GAVE). Frequently, multiple APC sessions are required, and some patients are refractory to APC ablation.
- CryoBalloon ablation is an efficacious and safe modality for the treatment of symptomatic refractory GAVE.

Introduction

Gastric antral vascular ectasia (GAVE) is characterized by longitudinal stripes of ectatic vessels that start at the pylorus and extend into the antrum or by a diffuse pattern of vessels.[1] Although it is an uncommon cause of bleeding (approximately 4% of nonvariceal upper gastrointestinal (GI) bleeding), it causes significant morbidity.[2] The most common presentation is iron deficiency anemia.[3] The etiology is unclear, but GAVE is often seen in patients with renal disease, cirrhosis, cardiac disease, autoimmune disease, and scleroderma.[1]

The recommended first-line treatment for GAVE is endoscopic ablation with argon plasma coagulation

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(APC).[1] However, multiple sessions are required and rebleeding rates can be as high as 60%.[4–6] Other modalities have been used to treat GAVE, including radiofrequency ablation (RFA) and liquid nitrogen cryotherapy (LNC).[7,8] Although RFA appears to be effective,[9–11] it may require up to four treatments per area treated. This is time-consuming and may lead to post-procedural pain. In addition, frequent removal of the RFA catheter is required to clean it and to reposition the probe to ablate different areas of the stomach. Frequent passage of the large catheter may be challenging and may predispose to orophyrangeal trauma and laceration at the gastroesophageal junction.[9,12] Spray cryotherapy has been successfully used to treat patients with GAVE.[13] Drawbacks to this technology include limited visibility in the stomach and concerns over ineffective venting of excess nitrogen gas.

Recently, a self-venting balloon-based cryotherapy has been introduced and is mainly used in treatment of Barrett's esophagus.[14,15] Advantages over spray cryotherapy include improved visibility via direct visualization through the balloon and no release of gas into the stomach. The use of the CryoBalloon for treatment of GAVE has been described in case report form; however, efficacy and safety data from larger series of patients are lacking.[16] It is our clinical experience that the CryoBalloon is safe and efficacious for use in APC-refractory GAVE. Thus, the aim of this study is to report the efficacy and safety of the CryoBalloon for patients with GAVE refractory to APC in three academic centers with experience using the device for this indication.

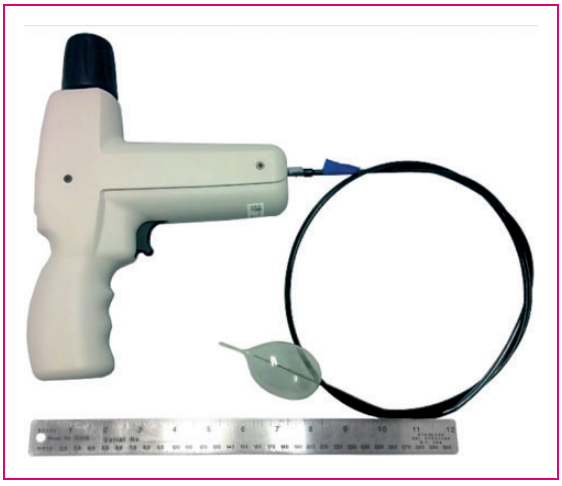

Figure 1. Nitrous oxide balloon cryotherapy system. (Image courtesy of C2 Therapeutics.)

Methods

Participants

This is a retrospective study on the use of the CryoBalloon (Coldplay CryoBalloon Focal Ablation System, C2 Therapeutics, Redwood City, CA (Figure 1)) in patients with GAVE refractory to APC. Patients were treated at three tertiary referral academic medical centers in the United States (Columbia University Medical Center, NY; Geisinger Medical Center, Danville, PA; Long Island Jewish Medical Center, NY). The study was approved by the institutional review (IRB) board at each site from September 5, 2016 to November 9, 2016. Written informed consent was not required by each patient, per each institution's IRB, as this was a retrospective study. The study protocol conforms to the ethical guidelines of the 1975

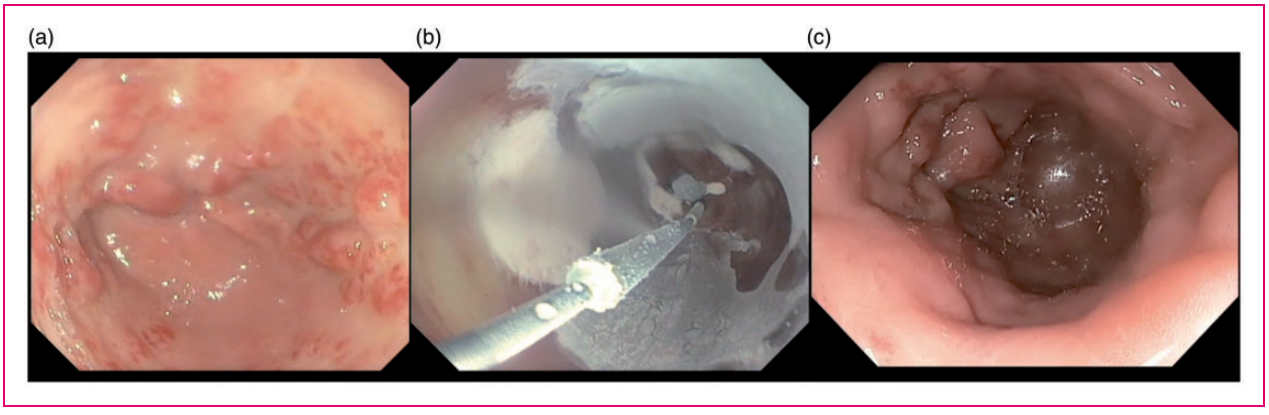

Figure 2. A patient with watermelon-type gastric antral vascular ectasia: (a) endoscopic view prior to treatment with CryoBalloon; (b) endoscopic image during CryoBalloon therapy; and (c) endoscopic image at three-month follow-up showing response to therapy.

Declaration of Helsinki as reflected in prior approval by the institutional review board at each site.

The main outcomes measured were technical, clinical, and endoscopic success. Technical success was defined as visualization of treatment effect in all intended areas of treatment. Clinical success was defined by transfusion independence and percentage of GAVE that was eradicated. Endoscopic success was defined as greater than 75% of the GAVE eradicated. Safety was defined with regards to adverse events. Acute adverse events were defined as events occurring during the procedure and recorded per the American Society for Gastrointestinal Endoscopy (ASGE) lexicon.[10] Late adverse events were defined as events identified after being discharged home from the hospital. These adverse events were captured by chart abstraction and review. Demographic information was collected, as well as prior medical and endoscopic management of GAVE. Refractory cases were patients who failed to respond to treatment with APC for a minimum of two separate endoscopic sessions.

Patients were included in this study if there was (1) endoscopic evidence of GAVE, (2) the presence of either anemia or evidence of overt upper GI bleeding (e.g. melena or hematemesis), (3) GAVE previously treated with APC, (4) a minimum of four weeks that had passed since the last treatment of APC, and (5) at least six months of follow-up. Patients were excluded if they were under 18 years old or were a member of a vulnerable population.

Specifics of CryoBalloon cryotherapy

The CryoBalloon Focal Ablation System consists of a balloon-tip catheter that attaches to a battery-powered, hand-held controller.[14] The controller contains a 23.5 g liquid nitrous oxide cartridge. The balloon catheter is advanced through the channel of a therapeutic endoscope (>3.7 mm channel) and the balloon is inflated to approximately 25–30 mm by pulling the trigger of the controller.[14] The inflated 3 cm long balloon contacts the mucosa to be ablated. Holding the trigger delivers nitrous oxide cryogen for a predetermined variable length of time that is preselected on the controller (Figure 2). The cryogen is contained within the balloon, and therefore a separate decompression tube is not necessary.

Endoscopic procedure/treatment

Informed consent was obtained from all patients. Moderate sedation with intravenous fentanyl and midazolam or monitored anesthesia care with propofol was administered based on physician preference and patient characteristics. The C2 Therapeutics single-use focal CryoBalloon, 3.6 mm diameter catheter (Redwood City, CA) was passed through a therapeutic endoscopic channel. The endoscope was advanced to the antrum of the stomach. The balloon catheter was connected to the portable, small, battery-powered handle that electronically controls the diffuser and holds the single-use liquid nitrous oxide canister. To allow visualization of the gastric mucosa through the transparent balloon, the trigger on the handle was pressed to deliver a one-second release of liquid nitrous oxide (“pre-puff”), which evaporates and inflates the balloon. The balloon catheter was positioned with its proximal end in contact with the endoscope tip. The “pre-puff” and resulting ice patch enabled visualization of the direction of the spray and allowed precise targeting. The cryogen was then directed to the targeted area by rotating the delivery catheter in the balloon clockwise or counterclockwise. After the “pre-puff,” the trigger of the handle was pressed and the cryogen was delivered for a preset number of seconds. A cryogen dosimetry of 10 or 14 seconds was used based on previous clinical experience and a clinical trial involving cryoablation in patients with Barrett’s esophagus.[15]

After cryoablation, routine medications were continued and diet was advanced as tolerated. Proton pump inhibitors or sucralfate (1 g three times a day, tablet or slurry) was prescribed according to each site’s standard postablation clinical protocol. Analgesics were not routinely prescribed. All patients had hemoglobin levels checked post-CryoBalloon therapy at three and six months. Patients who had ongoing symptoms of anemia had more frequent laboratory surveillance.

Data collection and analysis

All analyses were conducted using SAS version 24 (SAS Institute Inc, Cary, NC).

The data for the following variables were collected for each patient: age, sex, previous or concurrent treatments, adverse events, number of treatment sessions, and results of cryotherapy. All individuals and treatments were assessed for the safety analysis using the ASGE adverse events grading system.[10] Categorical variables were analyzed using chi squared analyses, and numerical variables were calculated using the mean or median where appropriate. A two-tailed p value of <0.05 was considered significant. Mean and standard deviation (SD) or mean and interquartile range (IQR) are reported for continuous variables. Proportions are reported for categorical variables.

Results

Twenty-three patients were included in the analysis. Patient characteristics can be found in Table 1.

Table 1. Patient characteristics.

	Total $N = 23$
Gender	
Female	16/23 (70%)
Male	07/23 (30%)
Age	
Mean	71.7
SD	10.2
Etiology	
Portal hypertension	10/23(43.5%)
Renal	1/23 (4%)
Collagen vascular	2/23 (9%)
Idiopathic	10/23(43.5%)
Presentation	
Anemia	23/23 (100%)
Melena	14/23 (61%)
Occult bleeding	6/23 (26%)
Pattern of GAVE	
Watermelon appearance	18/23 (78%)
Diffuse	5/23 (22%)
Percentage of antrum involvement	
0%–25%	1/23 (4%)
25%–49%	0/23 (0%)
50%–75%	5/23 (22%)
76%–100%	17/23 (74%)
Prior treatment	
APC	23/23 (100%)
RFA	7/23 (30%)

APC: argon plasma coagulation; GAVE: gastric antral vascular ectasia; RFA: radiofrequency ablation.

Sixteen patients were female and the mean age was 71.7 years (SD 10.2 years). All patients presented with anemia and 14 presented with melena. All patients were refractory to prior treatment with APC based on our criteria. Seven patients had also undergone RFA treatment, with no improvement, and were thus considered RFA refractory as well. The gastric antrum was involved in all patients and the gastric cardia in one. None of the patients had evidence of involvement elsewhere in the stomach and thus were consistent with GAVE, as opposed to portal hypertensive gastropathy, which can be seen throughout the stomach.[1,17] Seventeen patients were treated with initial 14-second dosing and six were treated with 10-second dosing. Sixteen patients (70%) had two treatments with the CryoBalloon and seven patients (30%) had one treatment. Out of the seven patients who had one treatment, three patients (50% of the 10-second group) had 10-second dosing and four (24% of the 14-second group) had 14-second dosing (50% vs 24%, $p = 0.25$).

Table 2. Patient outcomes.

	$N = 23$
Technical success (34 CryoBalloon procedures)	100%
Clinical success (defined as transfusion independent following CryoBalloon)	
At three months	11/23 (48%)
At six months	19/23 (83%)
Endoscopic success (defined as $\geq$75% of GAVE eradicated)	
At three months	9/23 (39%)
At six months	20/23 (87%)
Average number of blood transfusions per month prior to and post-initial CryoBalloon	
One year prior to CryoBalloon ablation	1.76 units
Six months after CryoBalloon ablation	0.31 units
Average increase in mean hemoglobin	
Six months after CryoBalloon ablation	2.55 g/dl

GAVE: gastric antral vascular ectasia.

CryoBalloon therapy outcomes can be found in Table 2. Technical success was achieved in all patients. Patients were transfused an average of 1.8 units/month one year prior to cryotherapy and an average of 0.3 units/month up to six months post-cryotherapy, which was statistically significant ($p < 0.001$). Average increase in mean hemoglobin at six months was 2.55 g/dl. At three months, 11 out of 23 (48%) were transfusion independent, and nine out of 23 (39%) had more than 75% of the GAVE eradicated. At six months, 19 out of 23 (83%) were transfusion independent, while 20 out of 23 (87%) had more than 75% of the GAVE eradicated.

In comparing the 10-second dosing vs the 14-second dosing, there were no statistical differences between the two groups in regards to clinical and endoscopic success at three months or six months. The three-month clinical success rates were 17% vs 59% (1/6 vs 10/17, $p = 0.08$) for the 10-second and 14-second dosing, respectively. The six-month clinical success rates were 67% vs 88% (4/6 vs 15/17, $p = 0.26$) for the 10-second and 14-second dosing, respectively. The three-month endoscopic success rates were 17% vs 47% (1/6 vs 8/17, $p = 0.2$) for the 10-second and 14-second dosing, respectively. The six-month endoscopic success rates were 67% vs 94% (4/6 vs 16/17, $p = 0.26$) for the 10-second and 14-second dosing, respectively.

There were no acute adverse events that were observed at the time of endoscopy or in the recovery area. On review of follow-up appointment notes, no late adverse events were discovered.

Discussion

APC is the mainstay of treatment for GAVE. However, around two-thirds of patients treated with APC remain reliant on blood transfusions.[18] This study shows that nitrous oxide CryoBalloon ablation is both efficacious and safe for patients with GAVE refractory to treatment with APC. The vast majority of patients achieved both transfusion independence and endoscopic response at six months (83% and 87%, respectively). At the three-month time point, 48% of patients were transfusion independent while 39% achieved endoscopic ablation success. Further prospective data are needed to understand the optimal length of therapy and factors predicting response.

There are many notable advantages to CryoBalloon therapy. Treatment requires a single passage of the endoscope. Only one ablation per site is required, minimizing ablation times. Another advantage is that ablation of the GAVE is clearly visualized throughout the entire process, which may not always occur with other cryotherapy platforms. After ablation, a deep erythema is visualized and selection of the next target site is straightforward. Finally, CryoBalloon ablation does not require a costly console or generator, and does not require time-consuming, cumbersome refilling of a cryogen. Thus, it is relatively easy to perform and may be accessible to a larger number of providers.

The anatomic distribution of GAVE is well suited for CryoBalloon ablation. GAVE usually involves the antrum but it can occasionally involve the gastric cardia, unlike portal hypertensive gastropathy, which can involve any part of the stomach.[1,17,19] It is this anatomical distribution of GAVE that makes the use of the CryoBalloon appealing for therapy. It is easier to appose the mucosa of the antrum and cardia against the balloon compared to other parts of the stomach.

In comparing CryoBalloon to RFA for APC-refractory GAVE, both modalities appear to be efficacious. In the largest prospective series evaluating 21 patients who underwent RFA for APC-refractory disease, the technical success and clinical success rates were 90% and 86%, respectively.[9] This is comparable to our study of 23 patients in which the technical and clinical success rates were 100% and 83%, respectively. The benefits of CryoBalloon over RFA include the portable nature of the device, the lack of expensive capital equipment (e.g. RFA generator), and the fewer number of ablations required in CryoBalloon over RFA. The CryoBalloon requires only one ablation per area treated vs up to four in RFA. Finally, the RFA probe is attached to the end of the gastroscope and may need to be removed frequently for cleaning. The CryoBalloon is inserted in the channel and is not removed until the procedure is completed.

LNC has also been studied in a limited capacity for GAVE. A prospective study of 12 patients, eight of whom were refractory to APC, showed LNC can be effective for GAVE eradication. Technical success was achieved in 89% while the mean rise in hemoglobin was from 9.9 to 11.3 g/dl. This small study is the largest study to date. In our experience, LNC for GAVE is challenging because of visibility issues. The lumen of the stomach is large and poor visibility occurs rather quickly. In addition, given the larger lumen, excess gas accumulation can occur quickly, despite the decompression tube. These challenges do not occur in the CryoBalloon thanks to the self-venting balloon design.

There are limitations to this study. The study is retrospective and thus subject to inherit limitations of this study design. One of these limitations is that retrospective studies may not capture minor late adverse events well as patients are not being prospectively followed to specifically screen for this. An example of this is post-procedural pain. Patients may have tolerable pain that keeps them out of the hospital but does affect their daily routine. This would not be captured well in this study design. That being said, these patients had close follow-up with their endoscopist for blood work and repeat procedures; no serious late adverse events were described in the patient charts. Another limitation is that the overall number of patients is small. However, one may consider this a relatively large cohort for a GAVE study, given that GAVE occurs in only 4% of nonvariceal upper GI bleeding.[1] Despite these limitations, the value and utility of CryoBalloon ablation for this cohort of patients was demonstrated in this study. Larger and prospective studies are needed to confirm our findings in the future.

In conclusion, this multicenter clinical experience suggests that nitrous oxide cryotherapy using a portable, novel contact focal cryoablation balloon is a safe and effective treatment option in the management of GAVE. Further studies must be conducted to evaluate the long-term effects of this modality in the management of GAVE. Comparative effectiveness trials might eventually determine the role of cryoablation in the treatment of GAVE and the potential role for its use earlier in the management of GAVE.

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Authors' contributions are as follows:
Conception and design (AAP, AJT, DLD, HSK, and AS).
Analysis and interpretation of the data (AAP, AJT, DLD, HSK, TPL, CL, and AS).
Drafting of the article (AAP, AJT, DLD, HSK, TPL, CL, and AS).
Critical revision of the article for important intellectual content (AAP, AJT, DLD, HSK, TPL, CL, and AS).

Final approval of the article (AAP, AJT, DLD, HSK, TPL, CL, and AS).

Declaration of conflicting interests

AJT, HSK, DLD are consultants for C2 Therapeutics.

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Ethics approval

Institutional review board approval was obtained from all participating centers. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institutions' human research committees.

Informed consent

Informed consent was not required, as this was a retrospective study.

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