



## ARGON PLASMA COAGULATION VERSUS BAND LIGATION IN GASTRIC ANTRAL VASCULAR ECTASIA IN CHRONIC HCV-RELATED LIVER CIRRHOSIS.

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### ABSTRACT:

**Background and aim:** Gastric antral vascular ectasia (GAVE) is a rare but serious cause of upper gastrointestinal bleeding. Argon plasma coagulation (APC) is used to treat GAVE, with considerable failure rate. The present study aimed to compare between APC and endoscopic band ligation (EBL) for GAVE treatment in HCV-related liver cirrhosis patients regarding efficacy and safety.

**Patients and methods:** The study included thirty patients with chronic HCV-related liver cirrhosis diagnosed with GAVE divided into two groups: group(1) 15 patients subjected to APC, group(2)15 patient had EBL .

Patients were followed up for 3 months with upper gastrointestinal (GI) endoscope, re- evaluation of their clinical status, complications and hemoglobin level.

**Results:** EBL group patients had statistically significant less number of treatment sessions ( $2.80 \pm 0.770$ ) vs. ( $4.87 \pm 1.13$ ) for APC group; ( $p=0.001$ ). EBL had significantly lower rate of recurrence during treatment and follow up period, less blood transfusion and hospitalization than APC group; ( $p<0.05$ ) In the first month, hemoglobin level was not significantly different in both groups, but within the second and third months follow up, hemoglobin level of EBL group showed persistent increase; ( $p<0.001$ )

**Conclusion:** Endoscopic band ligation is superior to argon plasma coagulation for GAVE treatment regarding less bleeding recurrence, less number of sessions needed, better hemoglobin level improvement, less blood transfusion, hospitalization and less major complications.

**Keywords:** argon plasma coagulation, endoscopic band ligation, gastric antral vascular ectasia

### 1. INTRODUCTION

Gastric antral vascular ectasia (GAVE) is a rare cause of bleeding from upper gastrointestinal tract (GI), accounting for approximately 4% of cases with non-variceal upper GI hemorrhage<sup>(1)</sup>. The vascular lesions are mainly in the stomach antrum, but rarely they may be found in the cardia<sup>(2,3)</sup>, duodenum, jejunum and rectum<sup>(4)</sup>. GAVE has a characteristic endoscopic pattern, which

appears as red stripes radially extending from the pylorus, known as watermelon type, predominantly seen in non-cirrhotic patients. They may be also arranged in a diffuse punctate-way, called honeycomb stomach that is common in liver cirrhosis<sup>(5)</sup>. Histologically, it appears as ectasia of mucosal capillaries, intravascular fibrin thrombosis, fibrohyalinosis around

capillaries of the lamina propria and spindle cell proliferation<sup>(6,7)</sup>.

The pathogenesis of GAVE could be related to mechanical stress, autoimmune mechanism or as a sequel of liver cell failure. It is now clear that portal hypertension does not cause GAVE, as reduction of portal pressure does not ameliorate the condition<sup>(8)</sup>. GAVE can complicate the course of many autoimmune disorders, as Reynaud's phenomenon, sclerodactyly, Sjogren's syndrome, primary biliary cirrhosis and systemic sclerosis<sup>(9,10)</sup>. Also, it is noticed in chronic renal failure<sup>(11)</sup>, bone marrow transplantation and cardiovascular diseases<sup>(12)</sup>

GAVE should be differentiated from portal hypertensive gastropathy (PHG), as the way of treatment is totally different. PHG mainly causes mucosal lesions in the fundus and corpus, while GAVE is often limited to the antrum.<sup>(13)</sup> GAVE is chiefly diagnosed by endoscopy. The majority of the patients are elderly females, who usually present with chronic iron deficiency anemia due to occult blood loss.<sup>(14)</sup> About 60 % to 70 % of patients become transfusion dependent as a consequence of chronic blood loss. In addition, patients with GAVE can experience overt bleeding as melena or even hematemesis.<sup>(15)</sup>

Many treatment approaches for GAVE induced GI bleeding have been identified, but the optimum method has yet to be determined.

Surgical approach, most commonly

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antrectomy, has high morbidity and mortality. Medicinal options as hormonal therapy (estrogen and progesterone), thalidomide (an agent of angiogenesis inhibition) as well as tranexamic acid (an antifibrinolytic agent) have been tried to control bleeding originating from GI vascular malformations, including GAVE.<sup>(16, 17)</sup> Endoscopic maneuvers such as cryotherapy, neodymium-yttrium-aluminum garnet (Nd: YAG) laser coagulation, argon plasma coagulation (APC), endoscopic band ligation (EBL), and radiofrequency ablation are techniques used to treat GAVE.<sup>(18)</sup>

The aim of this work was to compare between the efficacy and safety of argon plasma coagulation (APC) and band ligation (BL) of gastric mucosa in the management of chronic HCV- related liver cirrhosis patients with gastric antral vascular ectasia (GAVE) induced upper GIT bleeding.

## Patients and Methods

### Study design:

A prospective randomized study was carried out on thirty chronic HCV- related liver cirrhosis patients with gastric antral vascular ectasia (GAVE) induced upper GIT bleeding. The patients were referred to the Medical Research Institute, Alexandria University for upper gastrointestinal endoscopy. An approval from the local Ethics Committee of Faculty of medicine, Alexandria University (Serial Number, 0105001) and written consent from the patients were obtained before the study.

They were classified into: fifteen patients designated for argon plasma coagulation, (group 1 or APC group), and fifteen patients designated for endoscopic band ligation, (group 2 or EBL group).

Inclusion criteria were chronic HCV-related liver cirrhosis patients with GAVE- induced upper GIT bleeding.

Exclusion criteria were: Patients with upper GIT bleeding due to causes other than GAVE (for example, esophagogastric varices, peptic ulcer, gastroduodenitis, severe portal hypertensive gastropathy), as well as other causes of GAVE (for example, chronic renal failure, autoimmune diseases, bone marrow transplantation, or cardiac diseases.).

## Methods

All patients were subjected to:

- Detailed history taking with stress on history of upper GIT bleeding (hematemesis and/ or melena).
- Thorough clinical examination with stress on general signs of anemia (pallor and tachycardia), abdominal examination (hepatomegaly, splenomegaly and ascites) and signs of liver cirrhosis as jaundice, ascites, encephalopathy, and bleeding tendency.
- Laboratory investigations done before treatment included:
  - Complete blood picture blood urea, serum creatinine.<sup>(19)</sup>
  - Liver profile: serum albumin, serum bilirubin, serum transaminases and prothrombin activity.<sup>(19)</sup>
  - Hemoglobin level (repeated every month till 3 months post- treatment),
  - Serum HBsAg, HCV antibodies (3rd generation ELISA), HCV RNA by PCR.<sup>(20)</sup>

- Patients were classified according to the Child-Turcotte-Pugh (CTP) classification<sup>(21)</sup> to assess the degree of liver cirrhosis.
- Abdominal ultrasound: Using a 5 MHz sector transducer scanner - Siemens G 50 to assess the presence of liver cirrhosis, ascites, portal hypertension and splenomegaly.<sup>(22)</sup>

Upper GIT endoscopy: Diagnostic upper GI endoscopy was done for all patients using a video-endoscope Olympus XQ to identify the type of GAVE, whether diffuse or striped (water-melon) type.

## Therapeutic procedures

- 1-Argon plasma coagulation (APC) was applied for group 1 patients (fifteen patients). APC using an argon source coupled with high frequency generator (APC 300, ICC200; Conmed), and flexible 2.3mm diameter axial probes. The mean power output applied was 60 W and gas flow rates were from 1.5 liter to 2 liters per minute. The session aimed to ablate as much of the surface as possible, at least 80 % of the mucosa in diffuse lesion. The target of successful endoscopic therapy gained was appearance of white coagulum in place of the previous severely congested mucosa.
- 2-Endoscopic band ligation (EBL) was applied for group 2 patients (fifteen patients) using multiband ligator (Cook Medical). Ligation bands were applied to abnormally-appearing mucosa in the antrum. Treatment was applied first to the distal antrum at the pylorus. Then application of ligation bands was progressed proximally till as much as possible of the mucosa with lesions was treated.
- 3-After both procedures, patients received omeprazole (20mg per day for 7 days following endoscopic sessions) to help healing of the coagulated tissues /sites of band ligation.

## Follow up of the patients:

Patients of both groups were followed monthly for 3 months by upper GI endoscopy, history of bleeding recurrence (hematemesis or melena), hemoglobin level and need for hospitalization and blood transfusion.

## Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Student's t-test was used to compare between two groups of normally distributed quantitative variables, while Mann Whitney U test was used for abnormally distributed quantitative variables. The Chi-square test was used for categorical variables to compare between different groups. Fisher's exact test or Monte Carlo test were applied for correction of chi-square when more than 20% of the cells have expected count less than 5. Significance of the obtained results was judged at the 5% level.

## Results

### Demographic and clinicopathological data of the studied groups: Table (1)

Group I (APC group) consisted of 9 males (60%) and 6 females (40%), their age ranged between 45 and 65 years (mean of  $54.6 \pm 6.08$  years), while group II (EBL group) included 10 males (66.7%) and 5 females (33.3%), their age ranged between 47 and 70 years (mean  $58.07 \pm 6.90$  years), i.e. both groups were matching regarding age and sex.

Pallor was found in 8 patients (53.3%) of group I and 1 patient (6.7%) of group II, group I (APC group) had significantly higher prevalence of pallor than group II (EBL group) ( $p=0.014$ ).

In group I (APC group), 2 patients (13.3%) presented with hematemesis and 13 patients (86.7%) presented with melena, while in group II, 15 patients (100%) presented with melena with no statistically significant difference between both groups.

Among patients of group I (APC group), 4 patients (26.7%) were classified as Child class A and 11 patients (73.3%) as Child class B. Among patients of group II (EBL group) 3 patients (20.0%) were classified as Child class A, 11 patients (73.3%) as Child class B and 1 patient (6.7%) as Child class C. Both groups showed no statistically significant difference in severity of liver disease determined by Child-Pugh classification.

**Table (1): Demographic and clinicopathological data of the studied groups:**

	Argon plasma coagulation (APC) (n = 15)		Endoscopic Band ligation (EBL) (n = 15)		Test Sig.	of P
	No.	%	No.	%		
<b>Sex</b>						
Male	9	60.0	10	66.7	$\chi^2 = 0.144$	0.705
Female	6	40.0	5	33.3		
<b>Age (years)</b>						
Min. – Max.	45.0 – 65.0		47.0 – 70.0		t= 1.460	0.156
Mean $\pm$ SD.	$54.60 \pm 6.08$		$58.07 \pm 6.90$			
Pallor	8	53.3	1	6.7	7.778*	<sup>FE</sup> p=0.014*
<b>Child Pugh score</b>						
A	4	26.7	3	20.0	1.137	MC P= 1.000
B	11	73.3	11	73.3		
C	0	0.0	1	6.7		
<b>Type of GIT bleeding at presentation</b>						
Hematemesis	2	13.3	0	0.0	2.143	<sup>FE</sup> p=0.483
Melena	13	86.7	15	100.0		

$\chi^2$ : Chi square test

FE: Fisher Exact

t: Student t-test

MC: Monte Carlo

\*: Statistically significant at  $p \leq 0.05$

p: p value for comparing between the two groups

### Laboratory investigations of the studied groups: Table (2)

Both APC group and EBL group had no statistically significant difference in haemoglobin level (gm/dl) done at the beginning of the study; (mean  $10.10 \pm 0.83$  g/dl and  $10.67 \pm 0.88$  g/dl, respectively).

Also, there was no significant statistical difference between the studied groups in serum ALT (IU/L), AST (IU/L), prothrombin activity (%), albumin (gm/dl), bilirubin (mg/dl) or serum creatinine (mg/dl).

**Table (2): Laboratory investigations of the studied groups at the start of the study.**

	APC (n = 15)	EBL (n = 15)	Test of Sig.	p
<b>Blood urea(mg/dl)</b>				
Min. – Max.	19.0 – 100.0	25.0 – 101.0	U=	0.005*
Median	40.0	67.0	45.00*	
<b>Serum creatinine (mg/dl)</b>				
Min. – Max.	0.50 – 2.0	0.50 – 1.60	t=	0.430
Mean ± SD.	0.42 ± 1.05	0.35 ± 0.93	0.800	
<b>Hemoglobin (g/dl)</b>				
Min. – Max.	8.0 – 11.0	9.0 – 12.0	t=	0.081
Mean ± SD.	10.10 ± 0.83	10.67 ± 0.88	1.810	
<b>WBCs (x10<sup>3</sup>/cc)</b>				
Min. – Max.	3.40 – 10.50	3.60 – 9.50	t=	0.660
Mean ± SD.	2.37 ± 7.21	1.58 ± 6.89	0.445	
<b>PLT (x10<sup>3</sup>/cc)</b>				
Min. – Max.	100.0 – 220.0	95.0 – 201.0	t=	0.184
Mean ± SD.	32.98 ± 169.7	31.32 ± 153.7	1.363	

t: Student t-test

U: Mann Whitney test

WBCs: White blood cells

p: p value for comparing between the two groups

PLT: platelets

\*: Statistically significant at p ≤ 0.05

**Diagnostic UGIT endoscopic findings of the studied groups: Table (3), Figures (1, 2)**

Diffuse pattern of GAVE was present in 7 patients (46.7%) of APC group and in 7 patients (46.7%) of EBL group, while striped pattern was present in 8 patients (53.3%) of APC group and in 8 patients (53.3%) of EBL group with no statistically significant difference between both groups.

In APC group, 5 patients (33.3%) had F1 esophageal varices and 7 patients (46.7%) had mild portal hypertensive gastropathy (PHG), while in EBL group, 7 patients (46.7%) had F1 esophageal varices and 9 patients (60%) had mild PHG. Regarding both parameters, there were no statistically significant difference between both groups.

**Table (3): Upper GIT endoscope findings of the two studied groups:**

	APC (n = 15)		EBL (n = 15)		$\chi^2$	p
	No.	%	No.	%		
<b>GAVE</b>						
Diffuse pattern	7	46.7	7	46.7	0.00	1.000
Striped pattern	8	53.3	8	53.3		
<b>F1 esophageal varices</b>	5	33.3	7	46.7	0.556	0.456
<b>Mild PHG</b>	7	46.7	9	60.0	0.536	0.464

$\chi^2$ : Chi square test

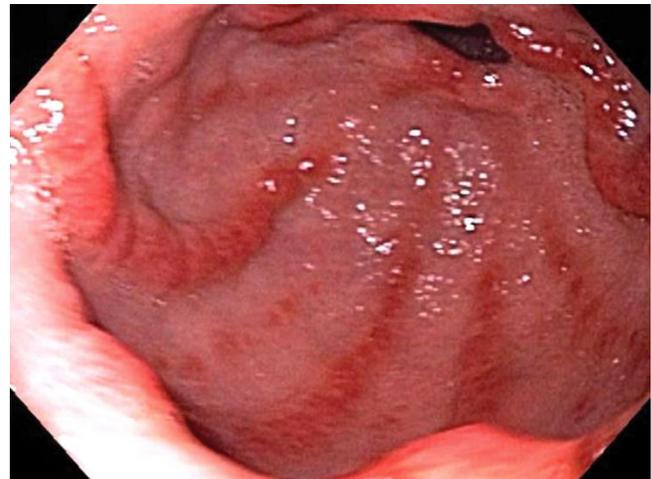
p: p value for comparing between the two groups

GAVE: Gastric antral vascular ectasia

PHG: portal hypertensive gastropathy



**Figure (1): Diffuse type GAVE.**



**Figure (2): Watermelon (striped) type GAVE.**

**Hemoglobin level in both studied groups over the study period: Figure (3)**

In the first month post treatment, hemoglobin levels of the APC and EBL groups were not significantly different (mean value of 10.10 ± 0.83 g/dl vs 9.0 – 12.0 g/dl, respectively). Hemoglobin levels in the second and third month post intervention, however, were significantly higher in EBL group than APC group (mean value of 11.03± 0.99 g/dl Vs. 9.11± 1.28 g/dl) and (mean value of 11.03±0.67 g/dl Vs. 9.27±1.18 g/dl), respectively. (p<0.001).

**Results of therapeutic endoscopy: Table (4)**

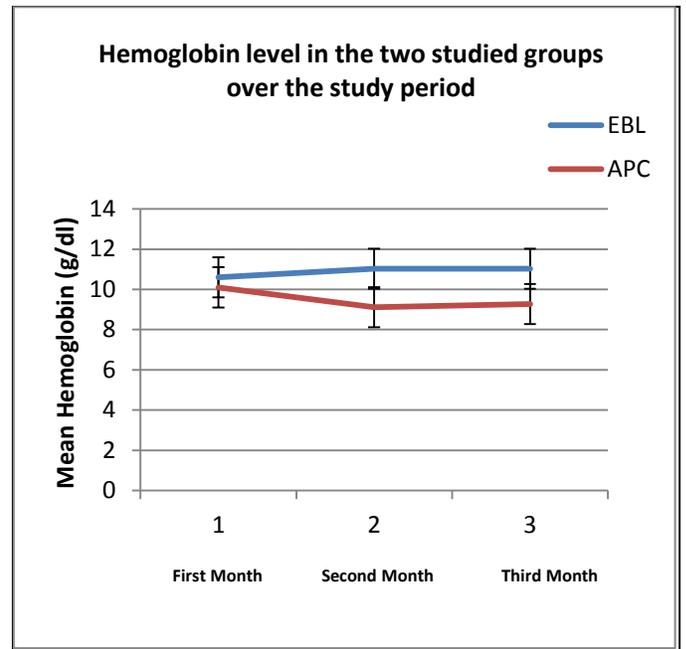
Group I, (APC group) needed significantly more sessions of APC than the number of band ligation(BL) sessions needed for group II (EBL group). The mean value of sessions number was 4.87 ± 1.13 session vs. 2.80 ± 0.77, respectively. (p=0.001).

Rebleeding (after endoscopic treatment) over the study period occurred in 8 patients (53.3%) in group I (APC group), while in group II (EBL group) it occurred in 2 patients (13.3%) only. APC group (group I) suffered from rebleeding more than group II (EBL group) (p= 0.020) over the study period.

Group I (APC group) received more blood transfusion which was performed in 7 patients (46.7%) vs. 1 patient (6.7%) in group II (EBL group) (p= 0.035).

Regarding hospitalization due to rebleeding during the study period, 10 patients (66.7%) of group I were hospitalized, while no patient of group II was in need for hospitalization

with a statistically significant difference between both groups (p<0.001).



**Figure (3): Comparison between the two studied groups regarding hemoglobin level over the study period.**

**Table (4): Number of sessions and re-bleeding, need for blood transfusion and hospitalization during the study period**

	APC (n = 15)		EBL (n = 15)		Test of Sig.	p
	No.	%	No.	%		
<b>Number of sessions</b>						
Min. – Max.	3.0 – 7.0		2.0 – 4.0		t=5.858*	<0.001*
Mean ± SD.	4.87 ± 1.13		2.80 ± 0.77			
<b>Rebleeding</b>	8	53.3	2	13.3	χ <sup>2</sup> =5.400*	0.020*
<b>Need for blood transfusion</b>	7	46.7	1	6.7	6.136*	<sup>FE</sup> p=0.035*
<b>Need for hospitalization</b>	10	66.7	0	0.0	15.00*	<0.001*

χ<sup>2</sup>: Chi square test

t: Student t-test

FE: Fisher Exact Test

p: p value for comparing between the two groups

\*: Statistically significant at p ≤ 0.05

**Discussion**

Gastric antral vascular ectasia (GAVE) is a rare cause of upper gastrointestinal bleeding. Its incidence is up to 4% of non-variceal upper gastrointestinal bleeding. (1) GAVE is usually located along the stomach antrum, appearing either in the form of longitudinal tortuous ectatic vessels “watermelon stomach” that is usually present in autoimmune disorders, or as “diffuse form,” that is commonly associated with liver cirrhosis.

The optimal treatment for GAVE is unknown. Before 1990, surgical antrectomy was the treatment of choice. However, surgery has a significant risk of mortality and morbidity in cirrhotic patients. Advances in endoscopic techniques allowed favorable options and better outcome for GAVE management. The most widely used in this scope was argon plasma coagulation (APC). Recently, endoscopic band ligation (EBL) is excessively being tried.

The aim of this work was to compare between the efficacy and safety of argon plasma coagulation (APC) and endoscopic band ligation (EBL) of gastric mucosa in the management of chronic HCV-related liver cirrhosis patients with gastric antral vascular ectasia (GAVE).

APC is a new of non-contact endoscopic technique that applies direct high-frequency monopolar current via ionized argon gas for the purpose of coagulation of tissue. It induces limited depth of injury. APC has been used successfully to cure GAVE, it has already showed adequate temporary control of GAVE-associated bleeding. However, it was proved that it is not adequately beneficial for medium and long-term treatment, as recurrence rate is high. (23)

Studies done to estimate long-term efficacy of APC in the management of GAVE showed disappointing results. Chiu and colleagues (24) studied APC in the management of GAVE,

and the recurrence rate was as high as 78.9%. Fuccio and colleagues<sup>(25)</sup> reported a relapse of GAVE in 15% of cases after a mean period of 7.7 months. Boltin and colleagues<sup>(4)</sup> demonstrated that APC treatment of GAVE was successful in only 25.8% of cases, in the form of absence of gastrointestinal hemorrhage, and there was only 30% increase in hemoglobin level during follow up. Most patients did not have long-term resolution of upper gastrointestinal bleeding and anemia. These outcomes are similar to our study, as 55.3% of patients who had APC as treatment of GAVE (group I) suffered from rebleeding during the study period. A large number of APC sessions was needed, ranging between 3-7 sessions for every patient with a mean value of  $4.87 \pm 1.13$  session. Moreover, 66.7% of patients needed hospitalization and 46.7% received blood transfusion during the study period.

Endoscopic band ligation (EBL) has recently emerged as an alternative treatment technique with better results and superiority as shown in some studies. The equipment used is a standard band ligator like that used for banding esophageal varices. The ligation bands are applied to the abnormal mucosa, starting from the distal antrum progressing proximally to involve as much of the abnormal mucosa as possible.<sup>(15)</sup> Endoscopic band ligation (EBL) is a safe and cheap modality.

In one randomized controlled study of the efficacy of EBL versus APC for GAVE treatment,<sup>(26)</sup> eighty-eight cirrhotic patients having GAVE were included and had received endoscopic sessions every 2 weeks. Results showed that a significantly less number of EBL sessions versus APC sessions needed for cure (2.98 vs. 3.48 ( $p < 0.05$ )) and a significant less number of blood transfusion packs needed in the EBL group ( $p < 0.05$ ). Complications were more manifest in the APC group, as eight cases 20.5% of the patients experienced adverse events (fever, abdominal distention, and epigastric pain), while three cases (13.6%) of the EBL group, had fever, minute bleeding from a post-banding ulcer and epigastric pain.<sup>(26)</sup>

Both Sato *et al.*<sup>(27)</sup> in 2012 and Prachayakul *et al.*<sup>(28)</sup> in 2013 concluded that EBL could be useful for cure of GAVE, because APC is associated with high relapse rate. In a retrospective study in 2013, Keohane *et al.*<sup>(29)</sup> concluded that EBL is a safe treatment of GAVE with adequate effectivity.

Similarly, in their study, Abdel Ghaffar *et al.* (2019) achieved in their study a superior effect of EBL over APC in terms of less number and time of sessions needed to fully obliterate the lesions, lower relapse rate, less need for hospitalization and less blood transfusion during the follow up period after treatment. However, mild complications such as abdominal pain and vomiting occurred more in the EBL group.<sup>(30)</sup>

These studies were in accordance with our results where the number of sessions needed for EBL group was ( $2.80 \pm 0.77$ ) session versus ( $4.87 \pm 1.13$ ) session for APC group. Rebleeding occurred in 13.3% for EBL group versus 53.3% for APC group, the need for blood transfusion was 46.7% for APC group versus 6.7% for EBL group and the need for hospitalization was 66.7% for APC group versus 0.0% for EBL group during the study period. ( $P < 0.05$ .)

In contrast, a study by Abd Al-Wahab *et al.* (2019) in a study included 18 cirrhotic patients who underwent APC versus 18

cirrhotic patients who had EBL as treatment for GAVE, both groups had nearly similar results with no statistically significant difference regarding hemoglobin level, recurrence after treatment, need for hospitalization or blood transfusion.<sup>(31)</sup>

The recurrent bleeding after APC treatment might be attributed to the limited depth involved in mucosal coagulation, which doesn't reach the submucosa affected in case of GAVE, thus not efficiently treated by APC. In spite that APC has a favorable side-effect profile for being non-contact method producing limited depth of mucosal injury, still major complications are reported such as gastric outlet obstruction and hyperplastic polyps.<sup>(15)</sup>

### Conclusion

Both endoscopic band ligation (EBL) and argon plasma coagulation (APC) are successful options for treatment of GAVE. However, endoscopic band ligation (EBL) is superior to argon plasma coagulation (APC) for eradication of GAVE regarding less recurrence rate of bleeding, less number of sessions needed, more improvement of hemoglobin level, less need for blood transfusion and hospitalization and absence of major complications.

Nevertheless, further studies are needed including larger number of patients and longer duration of follow up in order to document the efficacy and safety of EBL over APC in treatment of GAVE.

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