

Argon Plasma Coagulation versus Endoscopic Band Ligation in Treatment of Gastric Antral Vascular Ectasia in Cirrhotic Patients in Zagazig University Hospitals

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Background and study aim: The Gastric antral vascular ectasia (GAVE) is one of the causes of upper gastrointestinal bleeding and accounts nearly four percent of all non-variceal upper gastrointestinal hemorrhage. Although Argon Plasma Coagulation is the standard treatment of GAVE, EBL may be used in the treatment of GAVE. This study was done to evaluate the therapeutic effect of APC in comparison to EBL for the treatment of bleeding GAVE in cirrhotic patients.

Patients and Methods: Our study was conducted on 36 adult cirrhotic patients with bleeding from GAVE. Patients were divided into 2 groups: 18 patients in each group. Group I was subjected to APC and group II was subjected to EBL. All patients were followed endoscopically after the first endoscopic intervention for 6 months as well as their hemoglobin level had

been evaluated monthly during that period.

Results: There was a statistically non-significant difference between both treatment groups as regards cessation of bleeding, increase in hemoglobin levels, reduction of transfusion requirements, decreasing of hospital admissions or decreasing of endoscopic recurrence of GAVE during the follow-up period (6 months), but EBL group has a better result than APC group. The application of the EBL technique has significantly increased in the band related complications as hypertrophied polyps and post band ulcerations, which are decreased in the following sessions, in comparison to the APC technique, which had no complications-related.

Conclusion: EBL and APC are effective methods in the treatment of bleeding GAVE in cirrhotic patients.

INTRODUCTION

Gastric antral vascular ectasia (GAVE) is considered as one of the causes of upper gastrointestinal bleeding and accounts about four percent of all non-variceal upper gastrointestinal hemorrhage [1]. GAVE is seen typically in the antrum and rarely in other gastric sites [2]. It is represented by either redline stripes radially arranged from pylorus called as (watermelon stomach), or diffuse red spots called as (honeycomb stomach) [3]. Histopathology of GAVE is characterized by increased numbers and the diameter of mucosal blood vessels, fibromuscular hyperplasia, fibrin thrombi, and spindle cell proliferation are seen without inflammatory signs [14]. GAVE can be found in many diseases, like liver

cirrhosis, Raynaud's phenomenon, sclerodactyly, Sjogren's syndrome, primary biliary cirrhosis, systemic lupus erythematosus, systemic sclerosis, essential hypertension, ischemic heart disease, chronic renal failure, acute myeloid leukemia, and bone marrow transplant [26-28]. Argon plasma coagulation (APC) is characterized by thermal coagulation of the superficial blood vessels of the affected site. APC is a simple, safe and effective maneuver in the treatment of different forms gastric vascular ectasia lesions [4,5]. APC is considered the standard therapeutic modality of GAVE [15,16] It coagulates the ectatic vessels of the superficial layers of the gastrointestinal wall leading to hemostasis. Endoscopic band ligation (EBL) is used for the

treatment for esophageal varices because of the obliteration of the submucosal varices [6], EBL is used as an effective treatment for other gastrointestinal diseases [7,8]. Previous studies investigated the role of EBL in the management of GAVE and proved its superiority to APC [20,21]. This study was done to evaluate the therapeutic effect of APC in comparison to EBL for the treatment of bleeding GAVE in cirrhotic patients.

PATIENTS AND METHODS

Study design: A prospective randomized study. This study was conducted on thirty-six cirrhotic patients with overt or occult bleeding from GAVE attending the Tropical Medicine Department, Zagazig University Hospitals, from April 2017 till February 2018.

Patients and sample size:

The calculation of the sample size was done using a computer program (Epi info version 6.04). Thirty-six cirrhotic patients who meet the inclusion criteria were randomized alternatively to undergo APC or EBL and classified into two groups (age, sex, and severity of liver disease matched):

Group I: Eighteen patients were subjected to APC sessions.

Group II: Eighteen patients were subjected to EBL sessions.

Inclusion criteria:

- Adult cirrhotic patients.
- With overt or occult bleeding from GAVE.
- Characteristic endoscopic findings of GAVE: GAVE was limited to the antrum and its appearance either watermelon stomach or diffuse pattern.

Exclusion criteria:

- Patients with GAVE associated with medical conditions other than liver cirrhosis as scleroderma, bone marrow transplantation, chronic renal failure, familial Mediterranean fever, and leukemia.
- All causes of upper GIT bleeding other than GAVE.

Methods:

- **History taking:** All patients were subjected to:
 - Special habits as smoking, drug abuse.
 - History of medications.
 - Prior treatment of GAVE as a blood transfusion or hospitalization.

- Upper and lower gastrointestinal symptoms as hematemesis and/or melena.
- History of sclerotherapy or band ligation.
- Signs of liver cell failure as jaundice, ascites, encephalopathy, and bleeding tendency.

Clinical examination:

- General examination as jaundice, pallor and lower limb edema.
- Abdominal examination as liver, spleen, ascites, dilated abdominal veins, umbilicus, incisions, and hernias.

Laboratory investigations:

- Complete Blood Count (CBC) especially Hemoglobin (gm/dl) which was done before and after treatment. Hemoglobin was done every month till 6 months post-treatment.
- Liver biochemical profile: ALT, AST, total bilirubin, and albumin
- Coagulation profile (INR).
- Occult blood in stool: in patients with suspected occult bleeding from GAVE pretreatment (significant anemia with recurrent packed red cell transfusion) and during the follow-up period.

Abdominal ultrasonography:

- The liver was assessed for size, the regularity of outline, echogenicity, portal vein diameter, and collaterals.
- The presence or absence of focal lesions.
- Spleen size.
- Ascites if present.

Child's Pugh scoring:

It was applied for cirrhosis to obtain the severity of liver cell affection [12].

Upper gastrointestinal endoscopy:

- Patients came to the endoscopy unit after an overnight fast. Each patient was given intravenous sedation with midazolam before endoscopy.
- Upper gastrointestinal endoscopy was done by a single expert endoscopist using (Pentax EPM-3500 and Olympus evis extra III cv-190 video endoscope Tokyo Japan).
 - **APC:** Standard APC equipment was used, consisting of a high-frequency electrosurgical generator (ICC 350; ERBE, Tübingen, Germany), an argon source which is regulated automatically (APC 300) and APC probe.
 - **EBL:** EBL was carried out using a Saeed Multi-Band Ligator (Cook Medical, Winston-Salem, NC), and ligation bands were placed on the GAVE.

Follow up of the patients:

Patients in our study were followed after the first endoscopic intervention for 6 months as follow:

- Hemoglobin value.
- The following sessions were occurred according to an endoscopic picture of GAVE and its risk of bleeding.
- Follow up upper endoscopy.
- Post-treatment outcome data on re-bleeding, packed red cell transfusion, hospitalization, cessation of bleeding, follow-up endoscopy regarding recurrence of GAVE in both groups were compared.
- Cessation of bleeding.
- Change in hemoglobin levels, transfusion requirement, and hospitalization.

Statistical analysis:

Data in our study were collected, presented in tabulates and analyzed statistically using a computer program: SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Quantitative data were showed as the mean \pm SD & median (range), and qualitative data were given as absolute frequencies (number) and relative frequencies (percentage). Independent samples Student's t-test was used to compare between two groups of normally distributed variables while Mann Whitney U test was used for non-normally distributed variables. Paired t was used to compare between two paired groups. the Chi-square test or Fisher's exact test or McNemar test were used to compare the Categorical variables. P-value <0.05 was considered statistically significant (S).

RESULTS

Regarding the age distribution of the studied groups, the mean age \pm SD within the APC group was (60 \pm 11) compared to (65 \pm 9) within the EBL group. Concerning the sex distribution of the studied groups, the number of females within the APC group and the EBL groups was 3 (16.7%) and 7 (38.9%) respectively. the number of males within the APC group and the EBL groups were 15 (83.3%) and 11(61.1%) respectively. There was no statistically significant difference between both groups as regard, age, and sex.

There is an insignificant difference between both groups as regard causes of liver cirrhosis $p>0.05$. Child's class A was detected in 8 patients (44.4%) in the APC group and 9 patients (50%)

of the EBL group. Child's class B was detected in 5 patients (27.8%) in the APC group and 5 patients (27.8%) of the EBL group. Child's class C was detected in 5 patients (27.8%) in the APC group compared to 4 patients (22.2%) in the EBL group showing no statistically significant difference was detected between the two groups. There was no statistically significant difference between the two groups regarding the type of bleeding from GAVE.

Mean pre-treatment Hb (gm/dl): was 7.6 \pm 1.4 in the APC group and 7.5 \pm 2gm/dl in the EBL group which was statistically not significant between the two groups. Mean pretreatment hospitalizations: was 8 (44%) in the APC group and 7 (39%) in the EBL group which was statistically not significant between the two groups. Mean pretreatment transfusions: was 9 (50%) in the APC group and 7 (39%) in the EBL group which was statistically not significant between the two groups. There was no statistically significant difference between the two groups regarding the pretreatment endoscopic findings. There is a statistically insignificant difference in treatment sessions between both groups. As regard recurrence, there was no statistical significance between the two studied groups.

Regarding the incidence of complications, the result of the occurrence of complication demonstrated statistically significant difference more in EBL group than the APC group. There was no statistically significant difference between the two groups as regard hemoglobin level, hospitalization and blood transfusion, but less blood transfusion and hospitalization in EBL group. Regarding the mean hemoglobin (Hb) (gm/dl); the post-treatments mean Hb was significantly higher when compared to the pretreatment mean Hb. As it was 7.6 \pm 1.4 pretreatment compared to 8.7 \pm 0.9 post treatment (p-value 0.003) in the APC group. The post-treatment mean Hb was significantly higher when compared to the pretreatment mean Hb. As it was 7.5 \pm 2 pretreatment compared to 8.8 \pm 1 post-treatment (p-value 0.001) in the EBL group.

Table (1): Demographic and clinico-pathological feature of patients with GAVE pre-intervention

	APC (n=18) n(%)	EBL (n=18) n(%)	P value
Mean age (years)	60± 11	65± 9	0.13(NS)
Gender(male/female)	15/3	11/7	0.13(NS)
Pallor	16(88.9)	14(77.8)	0.6(NS)
Mean Hb (gm/dl)	7.6±1.4	7.5±2	0.9(NS)
Hematemesis & or melena	14(77.8)	15(83.3)	0.5(NS)
Creatinine Mean± SD (Median)	1.5±0.57	1.3±0.58	0.46(NS)
Previous endoscopy (EIS or EVL)	6(33.3)	6(33.3)	---
U.S. finding			
Portal vein dilatation	16(88.9)	18(100)	0.2(NS)
Collaterals	7(38.99)	6(33.3)	0.7(NS)
Cause of cirrhosis			
HCV	14(78)	16(89)	0.5(NS)
HBV	3(16.5)	2(11)	
Others	1(5.5)	0	
Child pugh classification			
A	8(44.4)	9(50)	0.9(NS)
B	5(27.8)	5(27.8)	
C	5(27.8)	4(22.2)	
Endoscopic finding			
Punctate GAVE	18(100)	16(88.9)	0.2(NS)
Esophageal varices	10(55.6)	11(61)	0.7(NS)

NS= not significant EIS: endoscopic injection sclerotherapy EVL: endoscopic variceal ligation

Table (2): Results after interventions

	APC (n=18) n(%)	EBL (n=18) n(%)	P value
Endoscopic recurrent			
Absent	1(5.6)	0	0.46(NS)
Improved	9(50)	13(72.2)	
Constant	5(27.8)	4(22.2)	
Worsend	3(16.7)	1(5.6)	
Median Number of session(range)	2(2-4)	2(2-3)	0.9(NS)
Complication(yes/no)	0/18	6/12	0.02(s)
Recurrence of GAVE	8(44)	3(17)	0.07(NS)
Cessation of bleed	10(56)	15(83)	
Pre-intervention Hb	7.6±1.4	7.5±2	0.9(NS)
Post-intervention Hb	8.7±0.9	8.8±1	0.9(NS)
P value	0.003(s)	0.01(s)	
Pre-intervention hospitalization	8(44)	7(39)	0.7(NS)
Post-intervention hospitalization	7(39)	2(11)	0.12(NS)
P value	0.99(NS)	0.12(NS)	
Pre-intervention transfusion	9(50)	7(39)	0.5(NS)
Post-intervention transfusion	7(39)	3(17)	0.14(NS)
P value	0.7(NS)	0.2(NS)	



Figure (1): Punctuate GAVE



Figure (2): Watermelon GAVE



Figure (3): APC applied to GAVE



Figure (4): EBL of GAVE

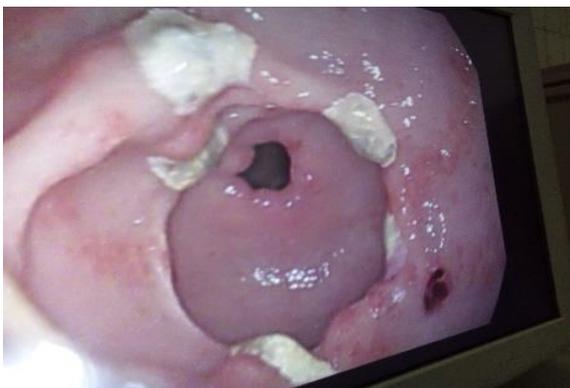


Figure (5): improved GAVE after EBL with ulcerations



Figure (6): improved GAVE after APC

DISCUSSION

Gastric antral vascular ectasia (GAVE) can cause occult blood loss or acute gastro-intestinal bleeding. GAVE can be found in liver cirrhosis patients, but may also be associated with other diseases as, autoimmune disorders, leukemia, chronic renal failure or bone marrow transplantation [13]. Characteristic endoscopic findings of GAVE: it was limited to the antrum and red spots were either aggregated in linear stripes (watermelon stomach) or diffusely spread without a background mosaic pattern (diffused GAVE) [14]. Argon Plasma Coagulation (APC) is considered the gold standard management of GAVE [15-19], it coagulates the ectatic vessels in the gastrointestinal tract leading to hemostasis.

The rationale for use of Endoscopic Band Ligation (EBL) is through its effect on the submucosal vascular plexus, this may explain why EBL may theoretically be effective at obliterating GAVE compared to APC [11]. A few years ago, multiple studies were done to investigate the efficacy of EBL in the management of GAVE and proved its superiority to APC [9,21]. In this study, we aimed to compare between argon plasma coagulation and endoscopic band ligation in treatment of GAVE in cirrhotic patients. Our research was carried out by many researchers before and the idea of our research was not a new one but our research was the first research on GAVE treatment in Zagazig University Hospitals.

In our study, the mean age of cirrhotic patients who presented with GAVE was 62.8 years. This agrees with similar studies performed on GAVE of cirrhotic patients and the mean age of patients was 65 and 59.5 years old, respectively [22,23].

In our study, there was a male predominance (72.2% of patients were males) with a ratio of male-to-female about 2.6:1, this male predominance was also observed in a similar study in cirrhotic patients in which GAVE predominantly affected males (69%) and (75%), with a male-to-female ratio of 2.2:1 and 3:1, respectively [18].

In this study, 12 patients (33.3%) out of 36 total patients had previous endoscopic injection sclerotherapy and /or endoscopic variceal ligation. This may be explained by the rise of pressure inside the submucosal vessels of the distal stomach with obliteration of collaterals in the lower esophagus and/or the proximal stomach which may have served as a reservoir for this

high pressure. This may subsequently lead to vascular ectasia and GAVE formation [10].

Liver cirrhosis in this study was mostly HCV-associated. It was detected in 30 patients (83.3%) out of 36 total patients. These findings are matching with similar previous studies in which the underlying cause of liver cirrhosis was HCV in the vast majority of patients [10]. This attributed that HCV is the commonest cause of cirrhosis in Egypt.

In our study 29 patients (80.6%) out of 36 total patients presented with acute overt blood loss (hematemesis and/or melena). This is in agreement with a study which stated that acute overt upper gastrointestinal bleeding appears to be more frequent in cirrhotic patients with GAVE [10].

Regarding the clinical manifestations, a large number of total patients in this study had pallor which was detected in 30 patients (83.3%) out of 36 total patients. Also, we found that patients in both groups had severe anemia, mean hemoglobin value was 7.6 ± 1.4 gm/dl in the APC group compared to 7.5 ± 2 gm. /dl in the EBL group and this was due to blood loss from GAVE. This is in line with Zulli et al. [13] who found that cirrhotic patients with GAVE frequently had significant blood loss and anemia often resulting in a repeated transfusion as well as in agreement with Naga et al. [18] who concluded that cirrhotic patients with GAVE presented mainly with anemia (79.3%) and overt gastrointestinal bleeding (51.7%).

In our study, most of the patients did not have advanced liver disease. From 36 total patients, 17 patients (47.2%) were Child A, 10 patients (27.8%) were Child B and 9 patients (25%) were Child C. So most of the patients are Child A and B, this is in agreement with a study done by Sato et al. [11] who reported that most of the patients in their study were child B. Abdelhalim et al. [10] stated that cirrhotic patients with GAVE had a significant liver disease with Child score mostly B and C.

Porto-systemic collaterals were detected in 13 patients (36.1%) out of 36 total patients, and esophageal varices were detected in 22 patients (61.1%) out of 36 total patients. This means that not all cirrhotic patients with GAVE had evidence of portal hypertension. Kamath et al. [24] concluded that portal hypertension in patients with cirrhosis was not important for the development of GAVE as patients did not respond to therapies that used

to reduce portal hypertension, such as TIPS or surgical shunt.

Most patients in the two groups have the punctuate type of GAVE, which was detected in 18 patients (100%) in the APC group as compared to 16 patients (88.9%) out of 18 total patients in the EBL group, while classic type of GAVE was detected in 2 patients (11.1%) in the EBL group. This could be explained by the fact that our patients were cirrhotic and the punctate type is the predominant type of GAVE in cirrhotic patients. Similar endoscopic appearance of GAVE was noted in previous studies on cirrhotic patients. Diffuse GAVE was seen in 75% of the patients in the study by Abdelhalim et al. [10] and in 76.5% of the patients in the study by Lecleire et al. [16].

Patients in both groups of this study had a high rate of cessation of bleeding from GAVE, where bleeding GAVE is controlled in 10 patients (56%) by the APC group and 15 patients (83%) by the EBL group have been controlled.

In this study, there is a significant improvement in hemoglobin level in both groups after intervention. In the APC group pre-treatment mean Hemoglobin was (7.6 ± 1.4) and post-treatment mean Hemoglobin was (8.7 ± 0.9), while in the EBL group re-treatment mean hemoglobin was (7.5 ± 2) and post-treatment mean hemoglobin was (8.8 ± 1). The blood transfusions had been reduced in both groups in this study after the intervention. In the APC group, 9 patients (50%), who complained from a recurrent blood transfusion, are reduced to 7 patients (39%). Also, in the EBL group 7 patients (39%), who complained from a recurrent blood transfusion, are reduced to 3 patients (17%).

In this study, the hospitalizations had been reduced in both groups after the intervention. A number of patients in the APC group and in the EBL group, who are hospitalized, were 8 patients (44%) and 7 patients (39%) and they are reduced to 7 patients (39%) and 2 patients (11%), respectively.

Patients in both groups of our study after the intervention had a high rate of cessation of bleeding, improvement in hemoglobin level at the end of the follow-up period as well as a reduction in the blood transfusion intervals and the number of hospitalizations. These results are in agreement with the study that has the same effect of both APC and EBL on GAVE with cirrhosis in the cessation of bleeding, improvement

in follow-up hemoglobin level, reduction in the blood transfusion intervals and the periods of hospitalization [10].

Many previous studies confirmed the efficacy of EBL in achieving a high rate of cessation of bleeding, significant improvement of hemoglobin level at the end of the follow-up period and a significant reduction in packed red cell transfusions and the number of hospitalizations [9,15].

At the end of the follow-up period, we classified the follow-up of GAVE endoscopically as absent, improved, constant or worsened. Most patients in both groups had significantly improvement of GAVE which was absent in only one patient (5.6%) in the APC group and improved in 9 patients (50%) in the APC group and 13 patients (72.2%) in the EBL group, while it was constant in 5 patients (27.8%) in the APC group and 4 patients (22.2%) in the EBL group. Few patients were had worsened GAVE which was detected in 3 patients (16.7%) in the APC group in comparison to one patient (5.6%) in the EBL group. No statistically significant difference regarding the endoscopic follow up of GAVE was found between both groups.

After 6 months the recurrence of GAVE in our follow up study was in 8 patients (44%) in APC group and 3 patients (17%) in the EBL groups. There was no statistically significant difference regarding the recurrence of GAVE between the two groups, but the recurrence of GAVE is less in the EBL group than the APC group. In similar studies, the recurrence of GAVE is more in the APC group than the EBL group [10,11].

A comparison of the post-treatment changes in different parameters between the APC group and the EBL group demonstrated a statistically insignificant improvement in the post-treatment hemoglobin, blood transfusion, and hospitalization. Post-treatment hemoglobin was 8.7 ± 0.9 in the APC group in comparison to 8.8 ± 1 in the EBL group. A number of patients with blood transfusion were 7 (39%) in the APC group in comparison to 3 (17%) in the EBL group. Hospitalization was 7 patients (39%) in the APC group in comparison to 2 patients (11%) in the EBL group, but the EBL group has a better result in decreasing blood transfusion and hospitalization than the APC group. This result is in agreement with other similar studies performed on GAVE in cirrhotic patients [10,11]. In our study, no complications

have occurred in the APC group, but in the EBL group 6 patients (33%) had complications which are not serious in form of hypertrophied polyps and post-band ulcerations, which are decreased in the following sessions. These complications were found due to the effect of the applied rubber bands. This result is in agreement with the complications (post-banding ulcers) after the application of EBL for the management of GAVE [11]. In some studies investigated the treatment of GAVE by APC, no complications related to the APC treatment have been reported [25].

CONCLUSION

EBL and APC are effective methods in the treatment of bleeding GAVE in cirrhotic patients, However, EBL proved to be a little superior to APC. Incidence of band-related complications (hypertrophied polyps and ulcerations) in EBL may be higher in the treatment of GAVE than APC, but these complications are not serious and decreased gradually in the following sessions. EBL is more available in the endoscopy centers and its financial cost is less than APC, so it makes the band ligation superior alternative to APC especially in countries with limited resources.

Limitations of our study: A small number of cases in our study explained by that were the number of cases of GAVE that present in our endoscopy unit at the study period time. Short period of follow up (6 months) was another limitation in our research; So, other studies with a larger number of cases with longer periods of follow up are recommended.

Conflict of interest: NO

Funding: NO

Ethical consideration: After approval of ethical committees, Faculty of Medicine Zagazig University. Informed consents were taken from patients included in the study.

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