Efficacy of argon plasma coagulation in the management of portal hypertensive gastropathy

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Introduction
Portal hypertension is defined as the pathological increase in portal pressure above 10mmHg due to increased portal blood flow as a result of increased mesenteric blood flow and/or increased portal vascular resistance. This causes dilatation of the portosystemic collaterals with formation of varices in the esophagus, rectum, around the umbilicus [1], the ovaries, and vesical, vaginal, intraperitoneal, and ectopic sites, commonly the small bowel, cecum, and stomal anastomosis [2]. Clinically, significant portal hypertension occurs when the portal pressure exceeds 12mmHg which is associated with an increased risk of variceal bleeding [3].

One of the complications of portal hypertension is portal hypertensive intestinal vasculopathy of which the most frequently seen is portal hypertensive gastropathy (PHG). This term denotes gastric mucosal changes as an endoscopic observation in cirrhotic patients with portal hypertension [4]. Histologically, there are dilated capillaries and venules of gastric mucosa. On the other hand, mucosal inflammation is infrequent and Helicobacter pylori association is infrequently seen or excluded [5].

PHG occurs in approximately 65% of patients with cirrhosis but can also occur in patients with non-cirrhotic portal hypertension. It is a marker of more severe liver disease and may predict variceal bleeding. Whether variceal sclerotherapy or banding exacerbates PHG is the subject of debate. PHG shows a tendency to occur in the gastric fundus and corpus [6].

Objectives:
Evaluation of the outcome and experience in 2 years of management of portal hypertensive gastropathy (PHG) by argon plasma coagulation (APC) in a cohort of Egyptian cirrhotic patients.

Methods: This study was conducted over a 2-year period from January 2011 to February 2013. Upper gastrointestinal endoscopy was performed to evaluate the degree and site of PHG. APC was applied to areas with mucosal vascular lesions.

Results: In total, 200 cirrhotic patients were enrolled; 12 patients were excluded due to death (n=6) caused by hepatic encephalopathy (n=3), hepatorenal syndrome (n=2), or chronic lymphatic leukemia (n=1), or did not complete the treatment sessions (n=6), so 188 patients completed the study. PHG was mainly fundic in 73 patients (38.8%), corporeal in 66 patients (35.1%), and pangastric in 49 patients (26.1%) (P=0.026). Patients were exposed to APC and received proton pump inhibitors together with propranolol at a dose sufficient to reduce the heart rate by 25% or down to 55beats/min. The mean (±standard deviation) number of sessions was 1.65±0.8; six patients needed four sessions (3.2%), 19 patients needed three sessions (10.1%), 74 patients needed two sessions (39.4%), and 89 patients needed one session (47.3%). Patients with fundic and corporeal PHG required the lowest number of sessions (P=0.000). Patients were followed up every 2 months for up to 1 year; the end point was a complete response with improved anemia and blood transfusion requirement which was achieved after one session in 89 patients (75.4%), two sessions in 24 patients (20.3%) and three sessions in five patients (4.3%). A complete response was more prevalent in patients with corporeal and fundic PHG (P=0.04).

Conclusions: After 2 years’ experience in managing PHG, we found that a combination of APC and non-selective beta blockers was highly efficacious and safe in controlling bleeding from PHG. In addition, APC alone is rapid, and effective in the control of PHG induced bleeding, especially when beta blockers are contraindicated.
Both mild and severe PHG can bleed acutely in nearly equal proportions, however, the bleeding is less severe than in bleeding from esophageal varices. Rebleeding is common in PHG after the initial episode, and chronic bleeding has been reported with a frequency of 11 – 30 % [7]. PHG is classified endoscopically according to McCormack et al. [8] who first described it in 1985; however, it was limited by lack of grading of intermediate endoscopic findings. In 1994, the New Italian Endoscopy Club (NIEC) proposed an alternative classification including a moderate aspect of PHG [9]. In 1996, the Baveno Score System was developed and attributed a higher risk of bleeding in patients with the severe form of PHG with odds ratio 2.56 [10]. PHG is classified into:

- **Mild:** ‘Scarlatina’ type rash; mosaic pattern; superficial reddening.
- **Severe:** Red spots indicate intramucosal hemorrhage (confluent or discrete), or diffuse hemorrhagic gastritis. PHG should be differentiated from gastric antral vascular ectasia (GAVE) which occurs in conditions other than cirrhosis and portal hypertension, such as chronic renal failure, connective tissue disorders, and bone marrow transplantation [11]. Characteristically, GAVE has linear columns of erythematous or raised mucosa with underlying tortuous ectatic vessels along the longitudinal folds in the antrum. Other patterns of GAVE are as speckled or diffused patchy erythema, honeycombing, and nodular antral gastropathy. In some cases, there is no clear distinction from PHG [12].

Histologically, PHG shows ectatic mucosal capillaries, whereas in GAVE, fibrin microthrombi, fibromuscular hyperplasia, and increased neuroendocrine cells are present in the lamina propria with a diagnostic accuracy of 85 % [13]. PHG is characterized by overt or chronic occult gastric mucosal bleeding. The annual incidence of overt bleeding from mild PHG is about 5 %, and it is 15 % in patients with severe PHG. Overt bleeding from PHG is usually manifested by melena and has a better prognosis than variceal bleeding with a mortality rate of less than 5 % per episode [14]. Occult bleeding occurs in about 8 % of patients with mild PHG and up to 25 % of patients with severe PHG with the development of severe chronic iron deficiency anemia that may require frequent hospital admissions and blood transfusions [15].

In the management of PHG, nonselective beta-blockers such as propranolol or nadolol appeared to be effective by decreasing portal hypertension in a randomized control trial. Somatostatin [16] and octreotide [17] have also been shown to reduce gastric perfusion temporarily. Bleeding in PHG was managed with portal decompression with surgical shunts or gastrectomy for chronic bleeding that was difficult to control. However, these options are becoming obsolete and have been replaced by transjugular intrahepatic portosystemic shunt and liver transplantation [18].

Argon plasma coagulation (APC) is an electrosurgical technique for the management of bleeding and the devitalization of tissue abnormalities. This is achieved by a noncontact thermal coagulation in which high frequency current is applied to the target tissue through an argon plasma jet creating effective hemostasis and a homogenous surface coagulation with a limited penetration depth. It was reported that the hemoglobin value improved and transfusion requirements decreased in patients with PHG after therapy with APC [19].

The aim of this study is to evaluate the outcome and examine our experiences in 2 years of management of PHG by APC in a cohort of Egyptian patients.

**Materials and methods**

**Patient selection**

This study was conducted at the Internal Medicine Department, Zagazig University Hospital, Egypt, a tertiary referral center, over a 2-year period from January 2011 to February 2013. The study was approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University. All the patients were reviewed and evaluated by full history taking, together with general and local examination by an internal medicine resident after written informed consent had been obtained from each patient.

The study included 200 patients with hepatic disease and with documented liver cirrhosis and portal hypertension proven by biochemical data and ultrasonographic criteria. They presented with upper gastrointestinal tract bleeding exclusively due to PHG, and were selected from 752 patients admitted with upper gastrointestinal tract bleeding in this predetermined period. They were admitted as a result of the first (n = 20 selected from 76 patients, i.e. 20/76) or recurrent episode of upper gastrointestinal tract bleeding (n = 40/150), or the follow-up after variceal endoscopic therapy (n = 80/401), or to investigate the cause of severe iron deficiency anemia resistant to conventional therapy (n = 60/125).

Patients were excluded from the study if they were non-cooperative or refused the procedure, if they were in an acute episode of hepatic encephalopathy, severe cardiopulmonary disease, chronic renal failure or hemodynamic instability, or if they had actively bleeding esophageal or gastric varices, or actively bleeding gastric or duodenal ulcers or malignancies.

**Thorough clinical examination**

All patients were thoroughly examined for vital signs, signs of portal hypertension such as dilated abdominal veins, or splenomegaly; signs of liver cell failure such as jaundice, ascites, lower limb edema, fetor hepaticus, flapping tremors, or spider angioma; and signs of renal, cardiac or respiratory diseases.

**Biochemical measurements**

The following tests were performed: liver function tests, prothrombin time, prothrombin concentration (%) and INR; kidney function tests including blood urea and serum creatinine, and complete blood count. For each patient, the Child–Pugh score was calculated.

**Abdominal ultrasonography**

All of the patients were examined using a real time gray scale device with a transducer having a frequency of 3.5 MHz. The patients were examined at bedside. A cirrhotic echo pattern was determined from the coarse nodular appearance and shrunken size with prominent caudate lobe. The following were noted: presence of ascites, portal vein diameter, splenic bipolar diameter, hilar varices, and splenic vein diameter.

**Upper gastrointestinal endoscopy**

After an 8-hour fast, all patients underwent gastro-duodenoscopy using a video endoscopic system (Pentax EPM-3500) with seda-
tion using intravenous midazolam in a titrated dose up to 0.1 mg/kg (5–10 mg).

During endoscopy, the following were evaluated: degree and site of PHG, presence of esophageal varices and their grade, fundal extension or presence of fundal varix, gastritis or duodenitis, erosions and ulcerations.

**Argon plasma coagulation**

The APC equipment consisted of an APC probe (lumen 1.5 mm, outer diameter 2.0 mm) advanced from the end of the working therapeutic accessory channel of the endoscope, a gas source, and a high frequency generator. The argon gas flow was set at 2.5 L/min. The electrical power output was adjusted to 60–90 W which was safe in relation to the local risk of perforation.

APC was applied to all areas of visible mucosal vascular lesions for about 1–3 seconds, with approximately 5 mm distance between APC probe and the gastric mucosal lesion. The probe could be applied axially or laterally. The end point of successful endoscopic therapy was production of a white coagulum which limits the depth of coagulation. The session duration was from 15 to 30 minutes. All patients received proton pump inhibitor therapy after the procedure to enhance mucosal healing.

**Follow-up of the patients**

Patients were followed up at 2-month intervals for 1 year by endoscopic surveillance, laboratory evaluation of complete blood count, and clinical evaluation of improvement in the initial symptoms. Endoscopically evaluated changes in the grade of PHG after the first treatment session were monitored. Definitive criteria for successful treatment were an improvement in the severity of PHG from endoscopic evaluation, cessation of the patient’s initial symptoms, cessation of blood transfusion, and an improvement in hemoglobin levels.

**Statistical analysis**

Collected data were analyzed using SPSS software, version 15 (SPSS Inc., Chicago, Illinois, United States). Results were expressed as mean ± SD. Categorical variables were analyzed using the $\chi^2$ test and continuous variables were analyzed using the Student’s t test or ANOVA when appropriate. $P<0.05$ was considered to be statistically significant.

**Results**

In total, 200 cirrhotic patients were enrolled in our study; 12 patients (6%) were excluded due to death (n=6) caused by hepatic encephalopathy in three patients (1.5%), hepatorenal syndrome in two patients (1%), chronic lymphatic leukemia in one patient (0.5%), or did not complete the treatment sessions (six patients; 3%). The baseline laboratory and endoscopic data for the 188 patients who completed the study (94%) are illustrated in Table 1. Their ages ranged from 34 to 67 years (mean 50.4±8.4 years) with a male predominance of 119/188 (63.3%). Of the 188 patients, 114 were referred to the emergency endoscopy unit due to melena and anemia (60.6%), and 74 patients were referred for elective upper gastrointestinal endoscopy as a follow-up after variceal endoscopic therapy (39.4%). All of the patients had splenomegaly on clinical examination with microcytic hypochromic anemia in 89 patients (47.3%) and normocytic normochromic anemia in 99 patients (52.7%) with a mean hemoglobin value of 7.3±1.3 g/dL; 92 patients showed ascites (48.9%), whereas 99 patients (52.7%) showed mild renal impairment with mean creatinine of 1.38±0.2 mg/dL.

Endoscopic evaluation of the patients revealed the distribution of severe PHG as shown in Table 1 where PHG was mainly fundic in 73 patients (38.8%), then corporeal in 66 patients (35.1%) and pangastric in 49 patients (26.1%) and that difference was statistically significant ($\chi^2=7.293, P=0.026$). The patients were further subclassified into three subgroups according to the distribution of PHG as shown in Table 2; there were highly significant differences among the three subgroups as regards hemoglobin level, iron indices, INR, and blood urea. All of the patients were exposed to APC in the first session and received proton pump inhibitors until the next session together with propranolol at a dose sufficient to reduce the heart rate by 25% of the initial level or down to 55 beats/minute which is sufficient to reduce the hepatic venous pressure gradient (HVPG) to less than 12 mmHg unless it is contraindicated in general as in ascites, chronic obstructive airway disease, or peripheral arterial disease; it was not prescribed in 92 patients (48.9%) under study who had ascites (34 patients (46.6%) in the fundic PHG group, 30 patients (45.5%) in the corporeal PHG group, and 28 (57.1%) in the pangastric PHG group) as shown in Table 2. Of the 92 patients with ascites, 56 patients had moderate ascites, 30 patients had marked ascites which was difficult to treat, and six patients had refractory ascites. In advanced cirrhosis with ascites, beta blockers may decrease renal perfusion, precipitate hepatorenal syndrome, and increase mortality, so they were not prescribed in this subset of patients.

The initial session duration extended from 20 minutes (fundic or corporeal PHG) up to 35 minutes (pangastric PHG). The mean (± standard deviation) number of sessions was 1.65±0.8, and the range of sessions was 1–4; six patients needed four sessions (3.2%), 19 patients needed three sessions (10.2%), 74 patients needed two sessions (39.4%) and 89 patients needed only one session with a complete response (47.3%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, years</td>
<td>50.4±8.4</td>
</tr>
<tr>
<td>Sex, M/F, n</td>
<td>119/69</td>
</tr>
<tr>
<td>Systolic pressure, mean ± SD, mmHg</td>
<td>94.2±15.2</td>
</tr>
<tr>
<td>Pulse, mean ± SD, beats/min</td>
<td>106.4±17.4</td>
</tr>
<tr>
<td>Spleen, n (%)</td>
<td>188 (100)</td>
</tr>
<tr>
<td>Ascites, n (%)</td>
<td>92 (48.9)</td>
</tr>
<tr>
<td>Melena, n (%)</td>
<td>114 (60.6)</td>
</tr>
<tr>
<td>Hemoglobin, mean ± SD, g/dL</td>
<td>7.3±1.3</td>
</tr>
<tr>
<td>Platelets, mean ± SD, ×10^3/µL</td>
<td>76.6±23.5</td>
</tr>
<tr>
<td>INR, mean ± SD</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Albumin, mean ± SD, g/dL</td>
<td>2.4±0.5</td>
</tr>
<tr>
<td>Total bilirubin, mean ± SD, mg/dL</td>
<td>1.9±0.5</td>
</tr>
<tr>
<td>AST, mean ± SD, IU/L</td>
<td>73.7±20</td>
</tr>
<tr>
<td>ALT, mean ± SD, IU/L</td>
<td>66.3±15</td>
</tr>
<tr>
<td>Creatinine, mean ± SD, mg/dL</td>
<td>1.38±0.2</td>
</tr>
<tr>
<td>Urea, mean ± SD, mg/dL</td>
<td>67±17</td>
</tr>
<tr>
<td>PHG distribution, n (%)</td>
<td></td>
</tr>
<tr>
<td>Fundic</td>
<td>73 (38.8)</td>
</tr>
<tr>
<td>Corporeal</td>
<td>66 (35.1)</td>
</tr>
<tr>
<td>Pangastric</td>
<td>49 (26.1)</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AST, aspartate aminotransferase.
The number of sessions varied according to PHG distribution. Patients with fundic PHG (n = 73) needed one session (n = 44) or two sessions (n = 29); patients with corporeal PHG (n = 66) needed one session (n = 45) or two sessions (n = 21); and patients with pangastric PHG (n = 49) needed two sessions (n = 24), three sessions (n = 19), or four sessions (n = 6) and the difference was statistically highly significant ($\chi^2 = 94.75, P = 0.000$).

The patients were followed up every 2 months for a duration up to 1 year. The end point was a complete response with improved hemoglobin levels ($P < 0.0001$).

A complete response was more readily achieved in patients with pangastric PHG as shown in Table 3 and Fig. 1 with improved hemoglobin levels (Table 4) and a decrease in transfusion requirements and ICU admissions.

A complete response to APC was independently associated with PHG distribution (odds ratio = 1.65, $P = 0.04$), 95.0%CI (0.0 – 0.073), and number of sessions (odds ratio = 0.41, $P = 0.000$), 95.0%CI (0.23 – 0.38).

### Discussion

Portal hypertension is a widespread abnormality in gastrointestinal mucosal microcirculatory integrity characterized by venous and capillary ectasia in the mucosa and submucosa. Portal hypertensive gastropathy (PHG) is one of the clinical conditions that can cause chronic gastrointestinal hemorrhage in patients with cirrhosis and is manifested by chronic anemia [20].

A reduction in portal pressure is the main target of treatment in PHG. Nonselective beta blockers are the most thoroughly investigated drugs for a sustained reduction in portal pressure. They should be continued on a long-term basis because discontinuing the drug frequently leads to recurrence of bleeding [21].

Argon plasma coagulation (APC) is a new, efficacious, safe, and easy-to-use method for the non-contact application of high frequency current through ionized and electrically conductive argon gas. It has been used successfully to treat vascular bleeding.
The total number of APC sessions was 1.9 ± 1.3. Treatment success overall success of APC was 86%, with only one recurrence of upper types of gastric vascular ectasia lesions in patients admitted for be considered before aggressive measures are taken [19].

Another study evaluated the role of APC in treating different types of gastric vascular ectasia lesions in patients admitted for upper gastrointestinal tract hemorrhage and revealed that the overall success of APC was 86%, with only one recurrence of upper gastrointestinal tract bleeding during the follow-up period. The total number of APC sessions was 1.9 ± 1.3. Treatment success for PHG was 81% with a rise in hematocrit from baseline values (P = 0.01), however, a limitation of the study was the low number of patients enrolled (n = 11) [23].

In the current study, we evaluated the efficacy of APC in the management of cirrhotic patients presenting with severe PHG. In total, 188 patients were enrolled and completed the study. They were divided into three groups according to PHG distribution: group I included 73 patients who had fundic PHG, group II included 66 patients with corporeal PHG, and group III included 49 patients who had pangastric PHG. After performing the APC and follow-up for 1 year, APC proved to be efficacious in controlling bleeding from PHG with no complications and with a significant improvement in hemoglobin levels and a decrease in blood transfusions and ICU admissions (P < 0.0001). In 89 patients with fundic or corporeal PHG, there was a complete response to control of bleeding in one session (75.4%), whereas six patients with pangastric PHG needed four sessions to achieve adequate control of bleeding (8.6%).

The combination of APC and nonselective beta blockers, unless contraindicated, may have a synergistic effect in controlling PHG. APC is a rapid, effective method for the control of PHG induced bleeding, especially when beta blockers are hazardous or contraindicated.

Some studies have suggested that PHG occurrence is transient after endoscopic sclerotherapy or banding and that the natural course of PHG after variceal banding seems to be milder than after sclerotherapy [24]. The combination of beta blockers with endoscopic variceal ligation therapy, which is recommended for secondary prophylaxis, has been shown to reduce the incidence of PHG [25].

The study was conducted on an adequate number of patients, however, it should be confirmed with a larger sample size and in patients with special conditions such as stable patients with hepatic encephalopathy, chronic renal failure, or cardiopulmonary disease.

In conclusion, after 2 years’ experience in managing PHG, we have found that the combination of APC and an adequate dose of nonselective beta blockers is highly efficacious in controlling bleeding from PHG, and that APC alone is rapid and effective in the control of PHG induced bleeding, especially when beta blockers are contraindicated.

Competing interests: The authors declare that no conflict of interest existed.

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