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LONG TERM FOLLOW UP OF ESOPHAGEAL VARICES PATIENTS' AFTER ENDOSCOPIC BAND LIGATION PLUS ARGON PLASMA COAGULATION: 3 YEARS FOLLOW-UP

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Keywords:
Portal hypertension, esophageal varices, Argon plasma photocoagulation, Endoscopic band Ligation, Rebleeding.

Abstract

Background: Endoscopic band ligation (EBL) is an established maneuver for secondary prevention of variceal bleeding. However, recurrence of varices and postbanding ulcers are frequent problems. This is the first retrospective study that determined the the long-term re-bleeding rate in patients with esophageal varices who had done endoscopic Argon plasma photocoagulation (APC) after endoscopic band ligation.

Aim: To determine the long-term re-bleeding rate of APC after endoscopic band ligation versus endoscopic band ligation alone for eradication of esophageal varices.

Methods: Two hundred patients with cirrhosis, and had performed endoscopic band ligation for eradication of varices were randomized to either argon plasma coagulation after band ligation or observation. Endoscopy was performed every 3 months to check for recurrence of varices in both groups. If varices were unremarkable twice, patients were moved to every six months throughout the whole period of the study.

Results: The 1-year, 2-year and 3-years rebleeding rates in the group of APC were 1%, 3% and 3%, respectively. While, rebleeding rates in the control group were 26%, 29% and 29% at 1-year, 2-years and 3-years respectively.

Conclusions: The present study confirms the effectiveness of APC in significantly reducing the rate of rebleeding after endoscopic band ligation.

Introduction

Portal hypertension is one of the most common complications of liver cirrhosis and remains the most important cause of morbidity and mortality in patients with cirrhosis **[1]**.

The prevalence of esophageal varices (OV) in patients with cirrhosis ranges between 24% and 80% **[2]** with an annual risk of variceal bleeding ranging betweent 4% to 15% and a fatal outcome in about 30% of patients during the first episode of bleeding **[3].**

Patients with esophageal variceal bleeding have higher rates of rebleeding, complications, and even more death rates than patients with bleeding peptic ulcer. Treatment procedures have included balloon tamponade, vasoconstrictors, and surgical intervention, but these measures was not associated with significant reduction of the rate of rebleeding, complications and mortality rates **[4].**

Both endoscopic sclerotherapy and band ligation are very effective in controlling acute OV bleeding and preventing rebleeding during hospitalization **[5]**. They are successful in achieving hemostasis in 80% to 90% of the patients with acute variceal bleeding **[6]**.

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Endoscopic band ligation (EBL) is an established maneuver for secondary prevention of variceal bleeding and it achieves eradication with fewer endoscopic sessions than sclerotherapy however, it is difficult to use during acute bleeding and more expensive **[7]**.

Argon plasma photocoagulation (APC) was suggested to prevent variceal recurrence and postband ulceration. This is the first retrospective study that determined the the long-term re-bleeding rate in patients with esophageal varices who had done endoscopic APC after endoscopic band ligation.

Methods

This study included Two hundred and seventy one patients with portal hypertension who had performed endoscopic band ligation for eradication of esophageal varices in the Gastro-Intestinal Endoscopic Unit in Tropical medicine department, Tanta University Hospitals, with upper gastro-intestinal bleeding. Seventy one patients were excluded as they did not meet the inclusion and exclusion criteria. The remaining two hundred patients were randomized to either argon plasma coagulation after band ligation or observation.

The study included Patients with portal hypertension presenting with a recent episode of esophageal variceal bleeding that didn't affect their conscious level. Patients with malignancy of any origin, including hepatocellular carcinoma, patients with terminal illness of any organ system, such as heart failure, uremia, or chronic pulmonary diseases were excluded from the study. Also, Patients who had other potential causes of upper GIT bleeding e.g. peptic ulcer or tumors or patients who had previous surgical treatment e.g. shunt operation or transjugular intrahepatic port systemic shunt were excluded from the study. Patients who met the inclusion and exclusion criteria were randomized to either groups by using consecutively numbered envelops that contain the treatment assignments. All patients were subjected to thorough history taking and complete clinical examination. Laboratory investigations were done for both groups of patients including complete blood picture; liver and renal function tests and viral markers for hepatitis C virus and hepatitis B virus using commercial enzyme-linked immunosorbent assay kits. All patients enrolled in the study also performed abdominal ultrasonography using (Toshiba 77025A MH 3.5) convex scanner.

Diagnosis of liver cirrhosis was based on Ultrasound examination and results of biochemical tests. Also, diagnosis of portal hypertension was based on ultrasound and clinical findings.
Finally, endoscopy was carried out under conscious sedation with evaluation for the grade of varices and recording of the risky signs e.g. red wale marks, cherry-red spots, adherent blood clots, white nipple signs, or erosions.
Group I included one hundred patients who received argon plasma photocoagulation after endoscopic band ligation. Endoscopic band ligation were performed until the varices shrank without red color sign. Then repeated treatment sessions were done at four weeks intervals until the varices were eradicated. Then, induction of fibrosis of the distal esophageal mucosa using argon source coupled with a high frequency generator (APC 300, ICC 200; ERBE) and flexible 2.3 mm diameter axial probes. Mean power output applied was 60w and gas flow rates ranged from 1.5 to 2.0 liters per minute. Circumferential coagulation of the entire esophageal mucosa was performed, starting from the esophagogastric junction, to 4 cm proximally.

Group II included one hundred patients who had done endoscopic band ligation. Banding was started at the gastroesophageal junction, and then continued proximally for several centimeters. The number of ligatures applied ranged from three to six. The repeated treatment sessions were given at four weeks intervals until the varices were eradicated.
All patients will be subjected to regular endoscopic follow up after eradication of varices every three months throughout the whole period of the study or or whenever recurrent bleeding occurred.

Statistical Analysis

Results were collected, tabulated and statistically analyzed by an IBM compatible personal computer with SPSS statistical package version 20 (SPSS Inc. Realesed 2011. IBM SPSS statistics for windows, version 20.0, Armnok, NY: IBM Corp.).

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Two types of statistical analysis were done:
a) Descriptive statistics e.g. was expressed in: Number (No), percentage (%) mean ($\chi 2$) and standard deviation (SD).
b) Analytic statistics e.g.
-Student's t-test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data.
-ANOVA test was used for comparison of quantitative variables between more than two groups of normally distributed data with LSD test as post Hoc test while; Kruskal Wallis test was used for comparison of quantitative variables between more than two groups of not normal distributed data with Tamhane's test as post hoc test.
-Chi-square test ($\chi 2$) was used to study association between qualitative variables. Whenever any of the expected cells were less than five, Fischer's Exact test was used.
-Z test was used to compare between r proportions (percentages).
-Pearson correlation was used to express correlation between normally distributed variables, while Spearman correlation was used to express correlation between not normally distributed or categorical variables.
-Kaplan Mayer statistics was used in survival analysis.

Results

As regard to baseline demographic and clinical data, there was no significant difference between both groups. Table (1) shows baseline demographic and clinical characteristics of both groups. Also, there was no significant difference between both groups as regard to baseline kaboratory data. Table (2) shows baseline laboratory findings in both groups.
Concerning the required therapeutic sessions, Number of sessions required were 4.71 ± 0.46 in group I versus (3.8 + 0.51) in group II. This is demonstrated in table (3).
The reported complication in our patients was pyrexia in 32% in patients in group I versus 9% in group II and pain was observed in 31% in patients in group I versus 12% in group II. In our study, After 3 years follow up, Rebleeding was observed in 3% of patients in group I and 29% in group II. Complications in both groups are shown in table (4). Also, mortality was fewer in group I than group II.

Discussion

This study included 200 patients with bleeding esophageal varices; they were randomly divided into two groups (I and II) Comparing the rebleeding rates and recurrence with combined bandligation followed by argon plasma photocoagulation (group I) versus bandligation alone (group II).

Endoscopic therapy is considered the optimal treatment for acute variceal bleeding and is also performed to prevent initial variceal hemorrhage and to prevent variceal recurrence **[8]**. EBL is widely used as an effective and standard treatment for esophageal varices by obliteration of the submucosal varices using a rubber band.
Currently, EBL is considered the gold standard for variceal ligation worldwide; however, it is not acceptable because of the high rate of recurrence associated with the technique. This is explainable by the fact that EVL does not obliterate the passage ways of varices and perforating veins **[9]**.

The reported rates of variceal recurrence after EBL range between 8–48%. Another commonly reported problem is postbanding ulcer. So, additional therapy should be considered after endoscopic variceal ligation to decrease the rebleeding rates **[10]**.

Endoscopic induction of mucosal fibrosis has been used as supplemental treatment for eradication of varices and for prevention of variceal recurrence. Mucosal fibrosis therapy should be undertaken as an adjunct treatment to band ligation **[11]**.

APC is a new modality of non-contact electrocoagulation that applies high frequency electronic energy into the tissue to cause defined thermal effects and which can be used for thermal devitalization of the tissue, as well as hemostasisSome results indicate that EVL combined with APC is superior to EVL alone **[11, 12]**.

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APC can be used for mucosal fibrosis therapy for the complete elimination of esophageal varices. We directed APC at the distal esophagus starting from the esophagogastric junction up to 5 cm proximally in order to interrupt the upward blood flow from the cardia and from the perforating branches running through the esophageal wall, and because it is also a common location for recurrence of varices. Application of APC over a wider area may cause various problems such as dysphagia and stricture; accordingly, we limited the target region to the distal 5 cm of the esophagus.

As regard to baseline demographic and clinical data, there was no significant difference between both groups.
We found that the required therapeutic sessions were 4.71 ± 0.46 in group I versus (3.8 + 0.51) in group II. Despite of more sessions in the first group, Patients in the second group reported significantly higher rebleeding which needed repeated endoscopy and increased morbidity and mortality in these patients. This was in accordance with a previous study which found a mean number of sessions in bandligation group was 3.7 versus 4.6 in combined group **[1].**

The reported complication in our patients was pyrexia in 32% in patients in group I versus 9% in group II and pain was observed in 31% in patients in group I versus 12% in group II.

Because APC is a substantially safe procedure, complication rates were reportedly low compared to other thermal methods of treatment. Pyrexia and retrosternal pain were common adverse events after APC for esophageal varices. Occurrence rates of those symptoms in our study were consistent with previous reports, and symptoms of all patients disappeared within a few days **[1].** However, other study showed higher rate of complications of argon plasma coagulation about 70% of the cases had transient fever that was alleviated rapidly with antipyretics **[13]**.

The recorded complications in our patients were less than those recorded by a previous study in Japan **[11].** They evaluated endoscopic induction of mucosal fibrosis by APC after band ligation for esophageal varices versus ligation alone. They studied 30 patients in each group and they found the most common complication in patients of the combined group to be pyrexia in 19 patients (63.3%). Development of severe strictures occurred only in one patient, which was confirmed by resistance to passage of the endoscope. This stricture was subsequently alleviated by treatment with an orally administered proton pump inhibitor. The frequency of retrosternal pain and sensation of esophageal obstruction was low and not significantly different between the two groups. They concluded that APC is generally a safe procedure, and endoscopic ligation of esophageal varices combined with APC is superior to ligation alone.

A previous study compared the use of APC after eradication of varices by band ligation in 16 patients versus ligation alone in 14 patients. During the course of the study, no serious complications were noted after argon plasma coagulation. A transient fever occurred in 13 patients and eight patients complained of dysphagia or retrosternal pain or discomfort **[14]**.

In our study, After 3 years follow up, Rebleeding was observed in 3% of patients in group I and 29% in group II, this may be explained by the fact that argon plasma coagulator is a device used for non-contact thermal coagulation of tissue. Endoscopic applications of APC continue to expand in the management of various gastrointestinal bleeding conditions, as well as in procedures in which ablation of tissue abnormalities is necessary.

The argon plasma jet is constantly attracted to tissue surface with the minimum impedance. Because tissue impedance is increased by cauterization and desiccation, the plasma jet automatically moves to other locations of low impedance, with the entire treated surface ultimately becoming a uniform zone of desiccation. As a result of this specific action with APC tissue damage is mild and perforation does not readily occur, so hemostasis and tissue coagulation can be undertaken safely on the thin-walled gastrointestinal tract **[15].**

Our result was not in accordanc with **Cipolletta et al., 2002** who reported that no variceal hemorrhage in the argon plasma coagulation group, whereas bleeding recurred in ligation group **[15]**.

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APC is thus theoretically well suited to mucosal fibrosis therapy, and elimination of varices and fibrosis of the mucosa can be expected. Hence, the use of APC as a supplemental treatment for the prevention of esophageal varix recurrence and bleeding appears reasonable **[16].**

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Table (1): Baseline demographic and clinical characteristics of both groups:

	Group (1)	Group (2)	P-value
Age	50.93 ± 7.53	49.55 ± 7.97	Non significant
Sex	Male 79 (79%) Female 21 (21%)	Male 81 (81%) Female 19 (19%)	Non significant
Jaundice:	23 (23%)	19 (19%)	Non significant
Ascites	29 (29%)	27 (27)%	Non significant
LL edema	37 (37%)	33 (33%)	Non significant
Child	A 21 (21%) B 67 (67%) C 12 (12%)	A 28 (28%) B 65 (65%) C 7 (7%)	Non significant

Table (2): Baseline laboratory findings in both groups:

	Group (1)	Group (2)	P-value
Hb (gm/ dl)	9.529 + 1.09	9.49+ 0.99	Non significant
WBCs(×103)/cmm	4.49 + 1.97	4.59 ± 2.00	Non significant
PLT(×103)/ cmm	98.38 + 58.85	102.9 ± 68.11	Non significant
AST (U/ L)	56.45+10.29	54.28 ± 15.37	Non significant
ALT(U/ L)	53.49 + 13.71	53.17 ± 18.16	Non significant
Serum albumin	2.82 + 0.48	3.21 ± 0.37	Non significant
INR	1.62 + 0.55	1.59± 0.53	Non significant
Total bilirubin	2.74 + 1.69	2.65 ± 1.66	Non significant
Urea (mg\100 ml)	39.24 + 14.46	38.36 ± 14.96	Non significant
Creatinine (mg/100ml)	1.22 + 0.46	1.18 ± 0.41	Non significant
Grade of varices	93% Grade III 7% Grade II	91% Grade III 9% Grade II	Non significant

Table (3): Number of sessions in both groups:

	Group (1)	Group (2)	P-value
Number of sessions	4.71 ± 0.46	3.8 + 0.51	P<0.05 (S)

Table (4): Recorded complications in both groups:

	Group (1)	Group (2)	P-value
Pyrexia	32	9	P<0.05 (S)
Pain	31	12	P<0.05 (S)
Rebleeding	3	29	P< 0.01(HS)

Table (5): Mortality in both groups:

	Group (1)	Group (2)	
Total mortality	9	12	P<0.05 (S)
Mortality due to rebleeding	1	2	P<0.05 (S)