

**ENDOSCOPIC BAND LIGATION VERSUS CARVEDILOL FOR PRIMARY PREVENTION OF BLEEDING OESOPHAGEAL VARICES CLINICAL, BIOCHEMICAL AND DOPPLER ULTRASONOGRAPHIC EVALUATION**

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**SUMMARY**

**Background:** Portal hypertension is one of the most devastating complications of chronic liver disease and is the most common cause of mortality and morbidity in patients with cirrhosis. Prevention of the first variceal bleeding is undoubtedly one of the most important issues in the treatment of portal hypertension. EVL is becoming increasingly competitive with B-blockers, owing to its low morbidity and high success rate.

**Aim of work:** The study was designed to compare the effectiveness of prophylactic EVL versus carvedilol for primary prevention of variceal bleeding among Egyptian patients.

**Patients and methods:** The study included 40 patients with chronic liver disease with grade III or IV varices and negative history of variceal bleeding, were divided into two groups, EVL group include 20 patients and carvedilol group include 20 patients. Both groups were subjected to thorough history taking, clinical examination, ECG tracing, laboratory investigations, abdominal ultrasonography, duplex ultrasonography and upper GI Endoscopy. Patients were followed up for one year.

**Results:** It was found that in the EVL group (20 patients) successful initial variceal obliteration was achieved in 14 patients (70%), variceal recurrence occurred in 4 patients (20%). Failure to reduce the size of varices was reported in only two patients (10%), these two patients had both portal and splenic vein thrombosis. Transient dysphagia was reported in 10% of cases and post banding ulcer was observed in 7 patients (35%) variceal bleeding before obliteration occurs in 3 patients (15%) and bleeding after obliteration in 2 patients (10%) variceal recurrence occurred in 2 patients (10%) and failure to prevent variceal bleeding in 4 patients (20%) and development of fundal varices occurs in one patient (5%) and as regard to duplex study of the EVL group. No significant change in PVD diameter before or after banding but there are significant increase in the duplex parameter as regard to CSA, MPBV and PBFV before and after therapy. Regarding to carvedilol group there was no significant change in the size of varices or grade of portal hypertensive gastropathy after carvedilol therapy but the number of bleeder during therapy (10%) was not significantly differs from that is reported in EVL group as regard to duplex parameters in carvedilol group there was significantly decrease in CSA, MPBV and PBFV result after 2 weeks of therapy and minimal increase occurs in those parameter after one year follow up but also remain significantly less than that is recorded before the start of therapy.

*There was no reported cases was intolerable to carvedilol therapy but 5 patients was hospitalized during therapy.*

**Conclusion** *carvedilol in a dose of 12.5 mg is a targeted dose which is effective as a portal hypotensive agent and is effective as EVL in the prevention of primary variceal bleeding*

## **INTRODUCTION**

Bleeding from oesophageal varices secondary to portal hypertension is a medical emergency with a high mortality rate. It is considered as the major complication of portal hypertension and occurs in up to 30 per cent of patients with chronic liver disease. The mortality rate associated with the initial bleed is 30-50 per cent (50% of these mortalities are in the first year of diagnosis), while mortality rate of subsequent bleeds is 30 per cent. Therefore an effective initial therapy to prevent initial variceal bleeding is highly desirable (**Ozsoylu et al., 2000**).

Within the short span of half a century, dealing with oesophageal varices has become highly differentiated with multiple therapeutic options. Endoscopic techniques are the optimal first-line treatment for acutely bleeding varices, either alone or in combination with pharmacological agents to reduce splanchnic blood flow and lower portal pressure. Such techniques are also optimal for subsequent long-term management to prevent re-bleeding when they fail, the percutaneous insertion of a transjugular intrahepatic portosystemic shunt usually achieves a rapid reduction in portal venous pressure with control of bleeding (**Beppu et al., 1981**).

Although, endoscopic injection sclerotherapy (EIS) provides effective treatment, there is potential for improvement as sclerotherapy is associated with variceal rebleeding in 20-50 per cent of patients and a high rate of local and systemic complications. A major disadvantage of EIS is oesophageal injury from inadvertent extravariceal leakage of sclerosant at the injection site, which may lead to ulceration, bleeding, perforation or stricture formation in a substantial proportion of patients. "Because of such limitations" endoscopic variceal ligation was developed as an alternative. The objectives of variceal band ligation are to provide an endoscopic treatment as effective as injection sclerotherapy but with the advantages of technical ease, quicker variceal eradication, fewer episodes of re-bleeding and safety, with fewer local and systemic complications (**Umehara et al., 1999**).

## **AIM OF THE WORK**

The study aims to compare the effectiveness of prophylactic band ligation versus carvedilol for prevention of primary variceal bleeding in high grade varices among Egyptian patients with portal hypertension and chronic liver diseases.

## **PATIENTS AND METHODS**

### **PATIENTS :**

The study included 48 patients with chronic liver disease and portal hypertension selected from the out patient clinic and Tropical Medicine department of Al-Husein University Hospital, Cairo, Egypt during the period from February 2008 to March 2009.

The patients was selected according to the inclusion criteria including liver cirrhosis (diagnosed on the basis of clinical , radiological , and laboratory parameters) and Oesophageal varices grade III , IV without previous variceal bleeding. Exclusion criteria includ patients less than 17 or more than 75 years, old, pregnant or lactating women, allergy to carvedilol therapy, presence of sever systemic illness (cardiovascular, respiratory and psychiatric disease) and sever hypotension. After an informed consent, patients were classified into two groups for primary prevention of variceal bleeding; EVL group including patients who subjected to endoscopic variceal ligation and Carvedilol group including patients who received carvedilol therapy.

### ***Methods***

The study was completed on 40 patients only, because 8 patients missed one or more visit of follow up schedule. Both groups were subjected to complete history taking, clinical examination, ECG tracing, complete blood picture, liver function tests, kidney function tests, abdominal ultrasonography, gastroscopy, and Dopplor Ultrasonography (with full comment on the Portal vein cross sectional area, portal vein mean velocity, portal vein flow volume, portal vein congestion index, splenic vein cross-sectional area and splenic vein mean velocity).

Doppler ultrasonography was done to all patients before and after the each session of variceal obliteration. The same parameters measured before EVL were measured again after the procedures by the same examiner, using the same machine and under the same conditions. following varical obliteration, patients were then enrolled in a follow up schedule that include their assessment every one month. Regarding to carvedilol group patients were given carvedilol in a dose of 12.5 mg, heart rate and blood pressure were checked after 12-24 hours, the dose was gradually increased after two weeks to reach 25mg daily. All patients in both groups were followed up every two weeks for 2 month then every month for one year

### **RESULTS**

A total number of 40 patients with liver cirrhosis and portal hypertension are followed from the period February 2008 to March 2009. The patients are classified into two groups, Group I (EVL group), include 20 patients and Group II (carvedilol group) include 20 patients.

In Group I (EVL group), the mean age  $51.5 \pm 8.1$ ; 13 (65%) male and 7 (36%) female. In Group II (carvedilol group), the mean age  $50.1 \pm 6.2$  , 11(55%) male and 9 (45%) female. There was no significant changes regarding to the clinical features between the studied group (Table 1)

**Table (1): Clinical Features Of The Studied Groups.**

Variables		EVL Group (20 patients)		Carvedilol Group (20patients)		p Value
Age (years)		51.50	SD $\pm$ 8.10	50.10	SD $\pm$ 6.20	NS
Gender	Males (NO)	13	56%	11	55%	
	Females (NO)	7	35%	9	45%	
<b>Aetiology of liver disease:</b>						
Post hepatitis B		2	10%	2	10%	NS
Post hepatitis C		10	50%	11	55%	
Schistosomiasis		0	0	1	5%	
Mixed Schistosomiasis& HCV		8	40%	6	30%	
Mixed Schistosomiasis& HBV		0	0%	0	0%	
<b>Child's grade:</b>						
Child A		8	40%	21	60%	NS
Child B		4	20%	4	20%	
Child C		8	40%	4	20%	

There was no significant changes regarding liver function tests, kidney function tests, CBC, ultrasonographic, and endoscopic findings before EVL or carvedilol therapy but, there was significant differences regarding the Doppler parameter study ( cross sectional area and portal vein flow volume ) before therapy in both group (Table 2).

**Table (2): Doppler Studies Of Both Groups Before Treatment.**

Variable	EVL Group NO / mean		Carvedilol Group No/ mean		p Value
<b>Portal Vein:</b>	<b>(20 patients)</b>		<b>(20 patients)</b>		NS
Thrombosed	2	10%	1	5%	
Diameter (mms)	15.12	$\pm$ 1.1	16.09	$\pm$ 1.0	NS
Mean Velocity (CM/SEC)	11.38	$\pm$ 3.1	17.9	$\pm$ 1.31	NS
CSA (cm2)	1.80	$\pm$ 0.49	2.23	$\pm$ 0.15	<0.05
Flow volume(ML/min)	1067	$\pm$ 238.2	2531	$\pm$ 250.3	<0.05
Congestion Index	0.13	$\pm$ 0.01	0.14	$\pm$ 0.02	NS
<b>Splenic Vein</b>					
Thrombosed	1	5 %	1	5%	NS
Diameter (MMS)	1.01	$\pm$ 0.32	1.11	$\pm$ 0.42	NS
Mean Velocity (CM/SEC)	14.12	$\pm$ 6.52	13.50	$\pm$ 6.33	NS
Area (CM2)	0.87	$\pm$ 0.43	1.01	$\pm$ 0.61	NS
Flow (MI/Min)	736.90	$\pm$ 517.62	823.31	$\pm$ 606.00	NS
Congestion Index	0.07	$\pm$ 0.04	0.08	$\pm$ 0.06	NS

Significant decrease in cross sectional area (CSA ), mean portal blood velocity ( MPBV) and portal blood flow volume (PBFV) was observed after two weeks of therapy in carvedilol group (Table 3). On the other hand there was significant increase in PBFV and MPBV after two weeks of EVL  $p < 0.05$  (Table 4)

**Table (3): Change In The Duplex Parameters After Two Weeks Of Therapy In Carvedilol Groups:**

Item	Mean ISD	p Value
PVD Before ttt (mm)	16.09 $\pm$ 1.0	NS
PVD after ttt (mm)	16.14 $\pm$ 1.0	
CSA Before treatment	2.23 $\pm$ 0.15	<0.05
CSA after Treatment (CM)	1.98 $\pm$ 0.7	
MPBV Before treatment	17.9 $\pm$ 1.31	<0.05
MPBV after Treatment (CM/SEC)	14.66 $\pm$ 0.89	
PBFV before Treatment PBFV after Treatment (M/miute)	2531 $\pm$ 250.3 2051 $\pm$ 120.2	<0.05

There are significant differences in duplex parameter after two weeks of carvedilol therapy except PVD where there is no significant difference.

PVD= portal vein diameter.

CSA= cross sectional area.

MPBV = Mean portal blood velocity.

PBFV= portal blood flow volume.

P < 0.50 = significant.

NS= Non significant.

**Table( 4): Changes Duplex Parameters in the EVL group Before and After Two weeks Therapy:**

Item	Mean ISD	p Value
PVD Before ttt (mm)	15.12 $\pm$ 1.1	> 0.05
PVD after ttt (mm)	15.10 $\pm$ 1.1	
CSA Before Treatment	1.80 $\pm$ 0.49	> 0.05
CSA after Treatment (CM)	1.71 $\pm$ 0.95	
MPBV before Treatment	11.38 $\pm$ 03.1	< 0.05
MPBV after Treatment (CM/SEC)	13.01 $\pm$ 3.9	
PBFV before Treatment	1067 $\pm$ 238.2	< 0.05
PBFV after Treatment (M/miute)	1311 $\pm$ 580	

With follow up of the patients on carvedilol therapy for one year, there was some increase in the level of CSA, PBFV and MPBV, but was still significantly less than its level before the start of carvedilol therapy (**Table 5**)

**Table (5): Changes In Duplex Parameter in the Carvedilol After One Year Of Therapy**

Item	Mean ISD	p Value
<b>PVD Before ttt (mm)</b>	16.09±1.0	NS
<b>PVD after ttt (mm)</b>	16.12±1.1	
<b>CSA Before treatment</b>	2.23±0.15	<0.05
<b>CSA after Treatment (CM)</b>	2.01±0.09	
<b>MPBV before Treatment</b>	17.9±1.31	<0.05
<b>MPBV after Treatment (CM/SEC)</b>	15.01±0.51	
<b>PBFV before Treatment</b>	2531±250.3	<0.05
<b>PBFV after Treatment (M/miute)</b>	2078±1314	

There is no significant changes in duplex parameters in the EVL group after one year as regard to PVD, CSA and MPBV but PBFV showed significant rise following obliteration. (Table 6)

**Table (6): Changes In Duplex Parameters In The EVL Group After One Year Of Therapy.**

Item	Mean ISD	P Value
<b>PVD Before treatment</b>	15.12±1.01	>0.05
<b>PVD after treatment</b>	15.02±1.01	
<b>CSA Before treatment</b>	1.80±0.49	>0.05
<b>CSA after Treatment</b>	1.75±0.55	
<b>MPBV before Treatment</b>	11.38±3.18	>0.05
<b>MPBV after Treatment</b>	12.88±3.71	
<b>PBFV before Treatment</b>	1067±1238.2	<0.05
<b>PBFV after Treatment</b>	1289±581	

The outcome after one year follow up in EVL group shows successful variceal obliteration in 14(70%) patients, with variceal recurrence in 4(20%) cases, but failure to achieve variceal obliteration was recorded in 2(10%) patients ,variceal bleeding occurs in 3(15%) patients before and 2(10%) after variceal obliteration, and development of fundal varices in one patient some adverse effects to EVL procedure was reported in 13(65%) patients ( Table 7 )

**Table (7) : Out Come After One Year Of EVL Therapy .**

Character	EVL
Patient hospitalised with complication (dysphagia,ulcer,coma)	13(65%)
Variceal bleeding before obliteration	3(15%)
Variceal bleeding after obliteration	2(10%)
Successful variceal obliteration	14(70%)
Variceal recurrence	4(20%)
Failure to achieve variceal obliteration	2(10%)
Failure to prevent variceal bleeding	4(20%)
Development of fundal varices	1(5%)
Death	0

The Outcome treatment with carvedilol after one year follow up shows well tolerability to therapy during the period of study , some minor complication in the form of mild hypotension at the start of therapy, nausea, and headache was recorded in 5(25%) patients . Variceal bleeding during carvedilol therapy reported in 2(10%) patients ( **Table 8** )

**Table (8) : Out Come Treatment After one year of carvedilol Therapy.**

Characteristic	Carvedilol
Variceal bleeding during therapy	2(10%)
Complication during therapy	5(25%)
Intolerance to therapy	0(0%)
Patient hospitalised	5(25%)
Development of fundal varices	0(0%)
Death	0(0%)

## DISCUSSION

Portal hypertension is one of the most devastating complications of chronic liver diseases and is the most common cause of mortality and morbidity in patients with cirrhosis, about 30%-60% of patients with cirrhosis develop esophageal varices and 30% of them bleed. These results were reported in many trials in which patients with medium-sized or large varices were included (**Gameel et al., 1996 Boyer, 1997; Primignani et al ., 2000**). Mortality due to the first variceal bleeding varies from

30%-50%, while mortality thereafter is dependent on the Child's class (**Mc Cormick 2001**).

Pharmacotherapy is currently the most widely accepted prophylactic therapy. More than 20 years have passed since the first report by Lebrech and co-workers showing that propranolol lowers portal pressure and reduces the risk of variceal bleeding. Non-selective  $\beta$ -blockers (propranolol, nadolol) was the most widely used drugs for preventing variceal bleeding, particularly in primary prophylaxis (**Lebrech et al., 1980; El-Sahly et al., 1989**).

Our data concerning that, technical characteristics of EVL were comparable with those obtained from other studies. The technique for EVL was the same applied by **Sarin et al., (1999)**, who used an average of 3-9 bands/session in early ligation, then fewer bands in subsequent sessions. In this study variceal obliteration was achieved using an average of 4-10 bands per session. The mean number of sessions in the current study was 4-10 ( $\pm 1.20$ ) sessions. This was slightly higher than that reported by **Sarin et al., (1999)** ( $3.31 \pm 1.10$  sessions) and in 3 randomized trials (**Sarin et al., 1996; Lay et al., 1997; Lo et al., 1999;**)  $3.33 (\pm 0.32)$  sessions.

Safety of the technique in this study is evidenced by the low incidence of complications encountered such as trivial transient dysphagia that was reported in only 2 cases (10%) immediately following ligation and then faded gradually. In a study by **Lo et al. 1999** the incidence of dysphagia was similar, being reported in 10.1% of cases. Another complication was the development of post banding ulcer occurred in 3 patients (15%). Throughout the one-year follow up period, none of our patients developed true strictures and none required dilatation. **Stiegmann et al., (1990)** reported that incidence of strictures was 2%. these were short strictures and readily dilated with a single pass of a dilator. **Wong et al., (2000)** has stated that the use of multi-ligator device has reduced - to a greater extent - the incidence of oesophageal tears caused by the over tube; a complication that was not reported in the current study.

In our study, initial variceal obliteration was reported in 14 patients 70% -close results were reported by **Lo et al., (1999)** 86% success. On the other hand, variceal bleeding was reported in 3 patients 15% who underwent EVL in this study. **Lo et al., (1999)** reported bleeding in 12.5% of cases while **Sarin et al., (1999)** reported it in 9% of the studied patients. The current study additionally reports failure to achieve variceal obliteration in two patients (10%) in whom the grade of varices couldn't be reduced despite repeated regular sessions of EVL. As considered by **Sarin and co-workers (1999)**, variceal recurrence is the main drawback of the technique of EVL, yet, they introduced a practical solution to this problem by early repeated banding, this would result in a much less incidence of recurrence.

In our study the incidence of variceal recurrence after obliteration was 20%. Similar results of recurrence of varices were reported by **Lui et al., (2002)** 23% of cases and **Sarin et al., (1999)** 22% of cases during a mean follow up of 13 months. **Lo et al., (2001)** reported that variceal recurrence in 47% of the treated patients after

a median follow up of 21 months. **Umehara et al., (1999)** reported higher results reaching 72%.

In the current study there was no bleeding-related mortality. Bleeding was reported in only 3 patients before obliteration (15%) Similarly **Omar et al., (2000)** reported absence of bleeding related mortality in patients undergoing EVL for primary prevention of variceal bleeding.

Comparing this to our results, variceal bleeding was reported in 3 patients (15%) before obliteration and two patient (10%) after obliteration, this can be explained by that the patients were not treated by mucosal protectors or anti-secretory drugs before obliteration, in addition to bad dietetic habits following each session. It is worth mentioning that in only one-of these 3 patients bleeding was due to sloughing of banded varices, while the origin of bleeding in the other was from the residual varices. Concerning the patients who bleed following obliteration, they did not attend good follow up regularly. When they developed melena the bleeding source couldn't be identified except in one of them and grade one residual varices were injected.

Few studies have assessed the relation between Doppler and EVL. Many studied were carried out on bleeders rather than non bleeders. Another point is that the results of Doppler studies seem rather conflicting and controversial. **Cioni et al. (1996)** reported that the absence of correlation between the portal vein maximum velocity and the degree of esophageal abnormalities detected on endoscopy in cirrhotic patients. In the same year, **Sekiyama et al.,(1997)**. found a significant difference between the portal vein mean velocity as well as flow volumes among bleeders and non bleeders (being significantly higher among bleeders). However the study refers to these parameters and the impact of the treatment on them. More specifically, in **2001, Yin et al.**, found that increased flow in the splenic vein may be the primary source of increased portal vein flow and may play a role in the development of esophageal varices. The mean ratio of the splenic vein to portal vein velocities may be valuable predictors of variceal bleeding. Also a low congestion index ( $<0.05$ ) and a mean portal vein velocity above 9 cm/sec., were at low risk of variceal bleeding as stated by **Sosa et al., (2000)**.

In our study the variceal obliteration has a tendency to increase the portal blood flow. There is a significant rise in the portal vein mean velocity and flow volume following variceal obliteration was observed, portal vein mean velocity increased from  $11.38 \pm 3.01$  (Cm/sec) before obliteration to  $13.01 \pm 3.9$  (Cm/sec) after variceal obliteration. Also the mean portal vein flow volume increased from  $1067 \pm 238.2$  M/min before obliteration to  $1311 \pm 580$  m/min after obliteration .

However, multiple response analysis for these parameters along the follow up period showed that the portal vein mean flow dropped again after the first 3 months and remained all through higher than pre-ligation levels. On the other hand there were no significant changes in the portal vein diameter or congestion index. Similarly, **Liu et al., (1997)** found that no change in the portal vein diameter slight

increase in its mean velocity after EVL suggesting that treatment with EVL may have a tendency to increase portal blood flow to the liver and stomach. Also **El- Beshalwy (1996)** reported that EVL resulted in a significant increase in the portal vein velocity and consequent portal vein flow volume after variceal ligation. These results were obtained for all patients in our study that comprised bleeder and non bleeders.

In our study, the increase in portal flow and velocity could be possibly explained by the reversal of blood flow in the para-oesophageal collaterals as a consequence of sudden occlusion of varices, causing the immediate rise. The gradual decline in the portal vein flow could be explained by the opening of other porto-systemic collaterals that accommodate the raised portal vein flow; a support of this explanation can be derived from the new development of re-canalized Para-umbilical vein after 3, 6 and 9 month of follow up.

The reflection of EVL on the severity of PHG seems trivial. In the current study at the end of 1 year follow up, there was no significant impact of EVL on PHG and only one patient developed fundal varices (5%), this agrees with the study of **Sarin et al., (1999)** who reported new development of fundal varices in only (5.3%) of patients. This trivial impact can be explained by the fact that following ligation, some blood flow persist at the gastro-esophageal junction preventing the near-total redistribution of the blood back to the stomach, this ameliorating the worsening of gastropathy and appearance of fundal varices. **Sarin et al., (1996)** found that the development of PHG was significantly lower after EVL when compared to EIS.

**Abdel- Rahim et al., (2000)** was reported that the severity of PHG increased significantly after EVL as compared to combined EVL and propranolol therapy. Recently, ultrasound pulsed Doppler has been accepted as a suitable method to monitor the magnitude of the acute and chronic hemodynamic variations which take place in the portal vein in response to pharmacological therapy of portal hypertension (**Albillos et al., 1997**). In our study, as regard to carvedilol group and its effect on the portal vein to prevent variceal bleeding, the dose of 12.5mg is a targeted dose of carvedilol which is effective on the portal vein pressure, this is based on a previous studies reported by **tripathi (2002)** and **De Bk (2002)** in a study on the hemodynamic effect of acute and chronic administration of low doses carvedilol in patient with cirrhosis and portal hypertension and they concluded that, 12.5mg is a target dose of carvedilol in portal hypertension of cirrhotic patients (conscious is required in patient with advanced liver diseases due to increase bioavailability of carvedilol). After two weeks of therapy by 12.5 mg carvedilol, there was significant decrease in cross sectional area from  $2.23 \pm 0.15$  (cm) before treatment to  $1.98 \pm 0.7$ (cm), also the mean portal blood velocity was decreased significantly from  $17.9 \pm 1.31$  before treatment to  $14.66 \pm 0.89$  two weeks after treatment and portal blood flow volume was decreased significantly from  $2531 \pm 250.3$  ml/min before treatment to  $2051 \pm 120.2$  two week after therapy, these parameters repeated after the end of one year and there were mild increase in these parameters but to degree less than the initial one which prevent variceal bleeding. At the end of therapy, variceal bleeding occurred in 10% of the carvedilol cases versus

25% in banding group, this agree with the **Tripathi (2009)** who record the rate of variceal bleeding in the banding arm was (20%) and carvedilol was (10%), also agree with the studies reported by **lay (2006)** and **schepke (2004)** who reported in a study of EVL versus beta-blocker in prophylaxis of first variceal bleeding in patient with cirrhosis, the bleeding in the banding arm varies between (14%-25%), the variceal eradication rate is 75% in banding which agree with the study by **Jutabha (2005)** who reported that variceal eradication reach 70% in a study comparing banding and beta blocker to prevent initial varical hemorrhage in cirrhotic with risk O.V. Carvedilol clearly had no adverse effect in our study because it has no change in the pulse and minimal reduction in blood pressure was noted in some cases. An observation noted in a previous homodynamic study was that of increased plasma volume and weight gain with Cavedilol as reported by **Banares (1999)**.

We did not find any different in the reporting of increased ascites in patients on carvedilol compared with VBL. We recognize that there may be a significant variation in the reporting of ascites. We did not perform HVPG measurement although we recognize that HVPG in useful in assessing efficacy and identifying exactly the responders to carvedilol however, high- quality studies demonstrate carvedilol to have a greeter effect on HVPG, with over 60% of patients having a homodynamic response, defined as a reduction in HPVg  $\leq 12$  mm Hg or by  $\geq 20\%$  of baseline, as reported by **Banares (1999, 2002)**.

**In conclusion**, our study demonstrates that low does carvedilol leads to a significant reduction in portal pressure and portal blood flow volume with minimal effect on systemic hemodyomics. The reduction in the portal pressure observed in this study is one of the largest reported in the literature to date and is comparable to the other pharmacological therapy and prove that carvedilol appears to have superior portal hypotensive effects and the drug is effective in preventing the first variceal bleeding and is well tolerated.

## **CONCLUSIONS**

- 1- EVL is an effective short term therapy for primary prevention of bleeding oesophageal varices but large number of sessions may be required to achieve variceal obliteration with high incidence of variceal recurrence.
- 2- Carvedilol in a dose of 12.5 mg is targeted dose which is effective on the portal vein pressure in cirrhotic patients with oesophageal varices .
- 3- Carvedilol was a potent portal hypotensive agent in reduction of portal pressure observed in this study comparable to the other pharmacological therapy in previous literature and the drug is effective and safe in prevention of first variceal bleeding and is well tolerated .

**REFERENCES**

- 1) **Abdel-Rahim A, Abdel-ElGhany M, El-Kholy B (2000)** : Band ligation alone versus Band ligation and propranolol in the management of bleeding oesophageal varices . The American Journal of Gastroenterology, 95 (9 ) : 2442 (abstract).
- 2) **Albillos A, Perez M, Cacho G et al ., (1997 )**: Accuracy of portal and forearn blood flow measurements in the assessment of the portal pressure response to propranolol. Journal of Hepatology , 27 : 496.
- 3) **Banares R, Moitinho E, Matilla A, Garcia-Pagan JC, Lampreave JL,Piera C,et al.,** Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. HEPATOLOGY (2002);36:1367-1373.
- 4) **Banares R, Moitinho E, Piqueras B, Casado M, Garcia- Pagan JC, De Diego A, et al.** Carvedilol , a new nonselective beta- blocker with intrinsic anti-Alphal-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. HEPATOLOGY 1999;30:79-83.
- 5) **Beppu K, Inokuchi K, Koyanagi N et al., (1981)**: Prediction of variceal hemorrhage by esophageal endoscopy Gastrointest Endosc;27(4):213.
- 6) **Boyer T (1997)**: Natural history of portal hypertension. Clin Liver Dis;1:31-44.
- 7) **Burroughs A, Jenkins W, Sherlock S (1983)**: Controlled trial of propranolol for the prevention of recurrent variceal haemorrhage in patients with cirrhosis. N Engl J Med; 309: 1539.
- 8) **Burroughs A,Patch D (1999)** : Primary prevention of bleeding from esophageal varices . N Engl J Med;340:1033 .
- 9) **Cioni J , Tincani E, Cristani A et al., (1996 )** : Does the measurement of portal flow velocity have any value in the identification of patients with cirrhosis at risk of digestive bleeding ; liver , 16 (2 ) : 84 – 7 .
- 10) **Dagradi A, Stempien S (1962)**: Symptomatic oesophageal sliding hiatus hernia. Am J Dig Dis; 7: 613.
- 11) **Dagradi A, Stempien S, Owens L (1966)**: Bleeding oesophageal varices: An endoscopic study of 50 cases. Arch Surg; 92: 944.
- 12) **De BK, Das D,Sen S, Biswas PK, Mandal SK, Majumdar**
- 13) **D,et al.** Acute and 7-day portal pressure response to carvedilol and propranolol in cirrhotics. J Gastroenterol Hepatol 2002;17:183-189.
- 14) **El-Beshlawy M (1996)**: Spleno-portal venous changes using Duplex-Doppler ultrasonography after variceal band ligation. M.Sc. Thesis, Tropical Medicine, Cairo University. 180.

- 15) **El-Sahly A, Hamad A, Abdel-Rahman H et al ., (1989 )** : The Effect of propranolol on portal hypertension in patients with schistosomal hepatic fibrosis . Egypt J Bilh ; 11 (1) : 123 .
- 16) **Gameel K, Waked I, Saleh S et al., (1996)**: Prophylactic endoscopic variceal band ligation (EVL) versus sclerotherapy (ES) for the prevention of variceal bleeding: an interim report of a prospective randomized controlled trial in schistosomal portal hypertension. Hepatology, 22:251:
- 17) **Gill R (1979)**: Pulsed Doppler with B-mode imaging for quantitative blood flow measurement. Ultrasound Med Biol; 5: 223
- 18) **Jutabha R, Jensen DM, Martin P, Savides T, Han SH, Gornbein J.** Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices. Gastroenterology 2005;128:870-881.
- 19) **Lay C, Tsai Y, Teg C et al., (1997)**: Endoscopic variceal ligation in prophylaxis of first variceal bleeding in cirrhotic patients with high-risk esophageal varices. Hepatology,25; 1346.
- 20) **Lay CS, Tsai YT, Lee FY, LaiYL, Yu CJ, Chen CB,et al.,** Endoscopic variceal ligation versus propranolol in prophylaxis of first
- 21) variceal bleeding in patients with cirrhosis . J Gastroenterol Hepatol 2006;21:413-419.
- 22) **Lebrec D, Nouel O, Cobric M et al., (1980)**: Propranolol; a medical treatment for portal hypertension. Lancet, 2: 180.
- 23) **Liu M, Li R, Li S et al., (1997)**: Color Doppler flow imaging study on the changes of collateral circulation between portal-superior vena cava and azygos vein before and after endoscopic ligation of the esophageal varix. Hunan Yi Ke Da Xue Xue Bao 1997;22(1):36-40 (abstract).
- 24) **Lo G ,Lai K, Chen; G et al., (1999)**: Prophy lactic banding ligation of high-risk esophageal varices in patients with cirrhosis: a prospective randomized trial. J Hepatol; 31:451.
- 25) **Lo G, Lai K, Cheng J et al., (2001)**: A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. Hepatology, 33(5):1060-4
- 26) **Lui H, Stanley A, Forrest E et al., (2002)**: Primary prophylaxis of variceal hemorrhage: a randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. Gastroenterology, 123(3):735.
- 27) **Mc Cormick PA, O'Keefe C.** Improving prognosis following a first variceal haemorrhage over four decades.Gut 2001; 49 :682-685.
- 28) **Moriyasu F, Nishida A, Ban N et al., (1986)**: Congestion Index of the portal vein. AJR;146:735.

- 29) **Omar M, Attia M, Mostafa I (2000):** Prophylactic band of large oesophageal varices. Theodor Bilharz research institute (unpublished data)
- 30) **Ozaki C, Anderson J, LiePerman R et al., (1988):** Duplex ultrasonography as a non-invasive technique for assessing portal haemodynamics. *Am J Surg*; 155:70.
- 31) **Ozsoylu S, Kocak N, Demir H et al.,(2000):** Propranolol for primary and secondary prevention of variceal bleeding in children with cirrhosis. *Turk J Pediatr*; 42(1):31.
- 32) **Primignani M, Carpinelli L, Sarin S et al., (2000):** Portal hypertensive gastropathy. In de Franchis R (ed) *Portal Hypertension III-Proceedings of the Third International Consensus Workshop on Definitions, Methodology and Therapeutic strategies*. Oxford, Blackwell Science.65
- 33) **Sarin S, Gupta R, Jain A (1996):** A randomized controlled trial of endoscopic variceal band ligation for primary prophylaxis of variceal bleeding. *Gastroenterol*;106: 975.
- 34) **Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS.** Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999;340:988-993 .
- 35) **Schepke M, Kleber G, Nurnberg D, Willert J, Koch L, Veltzke-Schlieker W, et al.** ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. *HEPATOLOGY* 2004; 40:65-72.
- 36) **Sekiyama T, Komeichi H, Magano T, Ohsuga M, Terada H, Katsuta Y, et al.** Effects of the alpha-/beta-blocking agent carvedilol on hepatic and systemic hemodynamics in patients with cirrhosis and portal hypertension. *Arzneimittelforschung* 1997;47:353-355
- 37) **Sosa J, Martin C, Moreno M et al., (2000):** Color duplex Doppler ultrasonography in the evaluation of the risk of esophageal varices bleeding in cirrhotic patients. *Gastroenterol Hepatol*; 23:466-9.
- 38) **Stiegmann G (1994):** Endoscopic management of esophageal varices.*Adv. Surg* 1994;27.209-31.
- 39) **Stiegmann G, Goff J, Sun J et al., (1990):** Endoscopic ligation of esophageal varices. *Am J Surg* 1990 Jan;159(1):21-5; discussion 25-6.
- 40) **Thakeb F, Zakaria M, Hunter M et al., (1988):** A study of the oesophagus by endoscopy and radiology after sclerotherapy. In Thakeb F. and Zakaria S. (eds.). *Gastrointestinal Endoscopy: an Egyptian view*, El-Sona El-Mohamadia, Egypt. 51.
- 41) **Tripathi D, Therapondos G, Lui HF, Stanley AJ, Hayes PC.** Haemodynamic effects of acute and chronic administration of low-dose carvedilol, a vasodilating beta-blocker, in patients with cirrhosis and portal hypertension. *Aliment Pharmacol Ther* 2002;16:373-380.

- 42) **Umehara M, Onda M, Tajiri T et al., (1999):** Sclerotherapy plus ligation versus ligation for the treatment of esophageal varices: prospective randomized study. *Gastrointest Endosc*; 50:7.
- 43) **Wong T, Pereira S, McNair A et al., (2000):** A prospective, randomized comparison of the ease and safety of variceal ligation using a multiband vs a conventional ligation device. *Endoscopy*,32(12):93.
- 44) **Yin-Y, Lu M, Huang J et al., (2001):** Color Doppler velocity profile assessment of portal hemodynamics in cirrhotic patients with portal hypertension: correlation with esophageal variceal bleeding. *J Clin Ultrasound*; 29:7-13.
- 45) **Zoller W, Gross M (1996):** Beta-blockers for prophylaxis of bleeding from esophageal varices in cirrhotic portal hypertension. Review of the literature. *Eur J Med Res*; 25(9): 407.

## مقارنة بين ربط دوالي المرئ و عقار الكارفيديلول في الوقاية من النزيف الأولي لدوالي المرئ دراسة إكلينيكية، كيميائية وبالموجات فوق الصوتية (الايكو) والمناظير

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يعتبر ارتفاع ضغط الوريد البابى واحد من أهم مضاعفات أمراض الكبد المزمنة إذ تمثل دوالي المرئ من 30% إلى 60% من هذه الحالات وبالتالي يكون المريض عرضه للنزيف بنسبة 35% وبدراسة إحصائيات الوفاة مع أول نزيف من 30% إلى 50% فى حين تكون الإحصائيات فى حالة تكرار النزيف بعد ذلك معتمدة على حالة الكبد ، تعتبر الوقاية من النزيف الاولى من دوالي المرئ بربط دوالي المرئ بلا شك واحدة من أهم سبل علاج إرتفاع ضغط الوريد البابى وتعتبر فى تنافس متزايد مع العلاجات العقارية لمثل هذه الحالات وبالأخص عقار الكارفيديلول الذى يعمل كمضاد لا إنتقائى لمستقبلات ألفا وبيتا الأدرينالية.

صممت هذه الدراسة للمقارنة بين فاعلية ربط دوالي المرئ و عقار الكارفيديلول من حيث الوقاية من النزيف الاولى لدوالي المرئ تضمنت الدراسة أربعون مريضاً يعانون من إرتفاع ضغط الوريد البابى بسبب تليف الكبد بشرط تواجد دوالي المرئ من الدرجة الثالثة والرابعة التى لم يسبق لها النزيف بأى صورة من الصور ثم أخذ التاريخ المرضى لهؤلاء المرضى مع عمل فحص إكلينيكى شامل وعمل البحوث المعملية وأيضاً فحص هؤلاء المرضى بالموجات فوق الصوتية العادية وبالموجات فوق الصوتية ( دوبلكس – دوبلر) ثم تقسيم المرئ فى حين تلقت المجموعة الأخرى العلاج بعقار الكارفيديلول للوقاية من النزيف الأولي لدوالي المرئ أظهرت النتائج إنخفاض تدفق الدم فى الوريد البابى وأيضاً فى الوريد الطحالي وأيضاً أنخفاض سرعة الدم فى الوريد البابى والطحالي عقب إعطاء المرضى عقار الكارفيديلول بجرعة 12.5 مجم بعد أسبوعين من العلاج على العكس إرتفاع هذه المؤشرات بعد أسبوعين من عمل ربط وقائى لدوالي المرئ فى مجموعة أخرى من المرضى ولم تظهر الدراسة أى تداعيات للعلاج بعقار الكارفيديلول على وظائف الكبد والكلى على مدار عام من المتابعة .

فى مجموعة ربط دوالي المرئ أظهرت النتائج نجاح ربط الدوالي فى 14 مريض ( 70 % ) وعادت الظهور فى 4 مرضى ( 20 % ) مع فشل الربط فى القضاء على الدوالي فى حالتين ( 10 % ) بمقارنة المجموعتين أظهرت الدراسة أنهما كانتا متقاربتين من حيث نسبة النزيف وكذلك معدل التكيف مع العلاج وأظهرت الدراسة إختلاف ملحوظ بين المجموعتين من حيث الأعراض الجانبية للعلاج حيث كانت مرتفعة إرتفاع ملحوظ فى مجموعة ربط دوالي المرئ 13 مريض ( 65 % ) مقارنة بمجموعة الكارفيديلول 5 حالات ( 25 % ) .

إستنتجت هذه الدراسة أن عقار الكارفيديلول هو وسيلة آمنة وفعالة فى الوقاية من النزيف الأولي لدوالي المرئ بالرغم من كونه وسيلة قد تعرض المريض لبعض الأعراض الجانبية إلا أن إلتزام المرضى وتكيفهم مع هذا العقار كان أفضل منه مع ربط دوالي المرئ إضافة على ذلك عدم قدرة المرضى على تحمل جلسات متكررة من المناظير وتعرض نسبة كبيرة منهم للنزيف وعدم تكيف الكثير منهم على هذه الوسيلة وتوصى هذه الدراسة بوجود الوقاية من النزيف الأولي لدوالي المرئ فى حالات الدرجة الثالثة والرابعة من دوالي المرئ.

أن عقار الكارفيديلول دواء فعال يوصى بإستعماله فى كل الحالات المتقدمة فى تليف الكبد وتؤكد على ضرورة ضمان إلتزام المرضى بالعلاج إذا ما أقر.