Losartan versus Endoscopic Variceal Ligation (EVL) In Primary Prophylaxis of Variceal Bleeding in Egyptian Cirrhotic Patients: prospective study

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Abstract: Introduction: esophageal varices (OV) is one of the major complications of portal hypertension in cirrhotic patients, bleeding form varices can be prevented using EVL, moreover blocking the activity of AT II (angiotensin II receptors) may have beneficial effects in lowering portal pressure. This study aimed at assessing Losartan versus EVBL in primary prophylaxis of variceal hemorrhage. **Patients & Methods**: 40 cirrhotic patients with esophageal varices of grade III to IV were classified into two groups, group I n=20 received Losartan therapy while group II n=20 received EVBL sessions, then patients were followed up after therapy for three months. **Results**: signs of impending variceal rupture disappeared in both groups with improvement in the grade of varices to become grade I in 100% in group II but only 17.6% in group I, Congestive gastropathy and ascites grades were improved in group I but deteriorated in group II. Conclusion: Both Losartan & EVBL are effective prophylactic to variceal hemorrhage in cirrhotic patients but Losartan was associated with much less complications.
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Keyword: Losartan, EVBL, congestive gastropathy, ascites, variceal hemorrhage.

1. Introduction

Portal hypertension commonly accompanies the presence of liver cirrhosis, and the development of esophageal varices is one of the major complications of portal hypertension[1]. Bleeding esophageal varices contributes to the estimated 32000 deaths annually attributed to cirrhosis[2]. Endoscopic techniques have been used to prevent variceal bleeding in cirrhotic patients with severe or moderate varices[3]. It has been reported[4] that variceal eradication is achieved with fewer endoscopic sessions and less frequent complications with EVBL than with sclerotherapy. A recent study has indicated that angiotensin II may elevate portal pressure via the enhancement of the adrenergic vasoconstriction effect and a direct contractile influence on stellate cells[5]. Blocking the activity of AT II may have beneficial effects in lowering portal pressure[6].

This study aimed at assessing the efficacy of Losartan, angiotensin II receptor antagonists versus EVBL as a primary prophylaxis of variceal bleeding in Egyptian cirrhotic patients

2. Patients and methods

Forty patients diagnosed as liver cirrhosis with esophageal varices grade III or IV attending to Endoscopy unit, Kasr El-Aini university hospitals were included in our prospective study after signing a written informed consent. Diagnosis of cirrhosis was based on physical findings, laboratory investigations and imaging findings. Patients with past history of bleeding esophageal varices or varices treatment and those with isolated fundal varices, HCC, partial or complete portal or hepatic vein thrombosis, hypotension or renal impairment were excluded from our study. Ultrasonographic examination (US) was performed for all cases by the same operator using Toshiba SSA-340A machine with a 3.5 MHZ convex transducer. Olympus GIF×Q30 endoscope was used for upper gastrointestinal endoscopic examination. Esophageal varices were graded according to Thakeb *et al.*[7], which was based on modification of Dagradi *et al.*[8]. Signs of impending rupture if present were recorded according to Beppu *et al.*[9]. Portal hypertensive gastropathy if present was graded according to Baveno III consensus[10]

Patients were categorized into two age and sex matched groups; Group (I) (n=20): patients received Losartan 50 mg daily for 3 months. Group (II) (n=20): EVBL was done for patients of this group until obliteration of oesophageal varices. EVBL was performed to patients of group II after an overnight fasting, Midazolam 5mg ampoule I.V was used for sedation. Multi-band ligators manufactured by the Wilson-Cook Medical GI endoscopy company were used. Complications such as: bleeding, dysphagia, fever or any respiratory problem were carefully recorded. Failure to achieve variceal obliteration was defined by failure to reduce the grade of varices after 3 sessions of ligation. Patients of both groups were followed up for 3 months clinically, by abdominal ultrasound (including Doppler assessment by the

same examiner, using the same machine and under the same conditions as before EVBL or medical treatment) and endoscopically.

Statistical analysis

All patients' data were tabulated using Excel XP. Data have been processed by SPSS (Statistical Package for Science and Society) version 12.0 for Windows XP. The descriptive statistics were presented with mean ± standard deviation (SD) for quantitative variables. All qualitative data were expressed by frequency (number) and percent. Comparisons between groups were done using Chi-Square test, Fischer's Exact test or Mcnemar test when appropriate for qualitative data but independent sample t test and Paired sample t test were used for normally distributed quantitative variables while Non parametric Mann Whitnney test and wilcoxon singed ranks test were used for abnormally distributed quantitative variables. In all tests, *P* value was considered significant if < 0.05.

3. Results

The baseline & follow up data of both groups are summarized in table (1) pretherapy data were compared and there was no statistically significant difference detected between both groups regarding their demographic data, clinical examination, laboratory investigations, MELD score, Modified Child's score, findings on examination using abdominal conventional ultrasonographic or Doppler ultrasonographic or upper gastrointestinal endoscopy, except that patients of group I had significantly higher grades of ascites and patients of group II had significantly higher levels of SVF (splenic vein flow) & SVV (spenic vein velocity).

On follow up (after the 3months) of patients of both groups it was reported that the esophageal varices grade was significantly improved in patients of both groups where 100% of patients of groups II showed grade I varices while this was encountered in only 17.6% of patients of group I and signs of impending variceal rupture disappeared from both groups. Moreover abdominal ultrasonographic examination revealed that the splenic volume was significantly decreased in patients of both groups, while the ascites grade significantly improved in patients of group I but it significantly deteriorated in group II. Regarding patients of group I it was found that the direction of portal vein blood flow showed a significant change to be heptopedal in all patients. In addition the S.V. diameter & S.V. CI significantly decreased. The congestive gastropathy grade showed significant improvement while patients of group II showed no significant change in these parameters after treatment except for the congestive gastropathy grade which markedly deteriorated.

Patients of group II showed significant deterioration in serum creatinine levels & all parameters of the CBC, while there was improvement in the total serum bilirubin, albumin & the PC levels. In addition there was a decrease in MELD scores, Splenic vein area and SVF on Doppler ultrasonographic examination while there were no significant change in these parameters in patients of group I, otherwise no statistically significant changes were found after therapy in both groups regarding the other studied parameters.

In group I only five patients (25%) showed significant improvement in the grade of esophageal varices to be grade I varices, on comparing those five patients to the rest of the patients in group I (75%) there was no statistically significant difference reported regarding all the studied parameters.

4. Discussion

Endoscopic elastic ligation (EVL) in eradicating esophageal varices has been shown to be an effective, safe, easy-to-do procedure with few untoward effects[11-12]. In our prospective study we found that in the EVBL group, initial variceal obliteration with disappearance of signs of impending rupture was achieved in all patients without critical complications or mortalities, however worsening of grade of congestive gastropathy & grade of ascites was obvious after follow up. In the Losartan group signs of impending rupture disappeared in all patients while 12 patients(70.5 %) showed significant improvement of the grade of varices. Improvement in the congestive gastropathy grade was achieved in 41.2% of patients as well as in the garde of ascites in 23.5% of patients, while mortality was reported in 3 patients (15%) within the first month of start of therapy following hepatic coma where their pre-therapy Child-Pugh score was C.

Losartan can reduce portal vein pressure, inhibit the activation of angiotensin II receptor 1 in the gastric submucous layer, and has therapeutic effect on PHG (portal hypertensive gastropathy)[13].

Table (1): Baseline & follow up data of patient in both groups:

	Group I			Group II			*p*-value
	Before therapy	After therapy	*p*-value	Before therapy	After therapy	*p*-value	
Age	53.2±5.8			49.65±3.4			NS
Sex (M/F)	45/55			45/55			NS
MELD	15.6±5.2	15.18±6.22	NS	14.1±4.93	12.45±3.77	0.005	NS
Child (A/B/C)	20/25/55	11.8/29.4/58.8	NS	15/35/50	25/50/25	NS	NS
Spleen longitudinal diameter	18.6±2.82	18±3.18	NS	18.9±3.9	18.96±2.31	NS	NS
Spleen volume	445.1±316.9	325.38±145.7	0.035	564.2±427.6	439.93±330.5	0.001	NS
Ascites (No/mild/moderate/marked)(%)	35/0/60/5	41.2/23.5/35.3/0	0.046	35/30/35/0	25/20/30/25	0.005	0.04
Portosystemic collaterals(%)	40	35.3	NS	75	75	NS	NS
Hepatic veins flow pattern (%) TRIPHASIC/BIPHASIC/MONOPHASIC	60/15/25	29.5/0/12	NS	60/10/30	40/0/60	NS	NS
Portal vein blood flow direction% Bidirectional/hepatfugal/hepatopedal	15/30/55	0/0/100	0.005	0/25/75	0/35/65	NS	NS
PV diameter (cm)	14.26±1.53	14.14±1.43	NS	14.86±1.67	14.94±1.46	NS	NS
PV area (cm²)	1.59±0.32	1.58±0.32	NS	1.75±0.41	1.77±0.37	NS	NS
PVF (ml/min)	848.19±2.19	918.09±244.5	NS	923.47±184.9	893.47±182.6	NS	NS
PV velocity (cm/sec)	8.95±2.19	9.61±1.46	NS	8.87±1.21	8.52±1.56	NS	NS
PV CI(cm. sec)	0.188±0.058	0.167±0.036	NS	0.203±0.067	0.217±0.074	NS	NS
SV diameter (cm)	11.09±2.42	9.65±1.69	0.029	11.43±2.35	11.22±1.6	NS	NS
SV area (cm2)	1.01±0.51	0.77±0.23	NS	1.19±0.45	1±0.28	0.033	NS
SVF (ml/min)	502.01±254.97	436.86±231.5	NS	772.53±349.5	616.4 ± 262.7	0.006	0.009
SV velocity (cm/sec)	8.44±2.66	9.1±2.84	NS	11±3.63	10.05±2.18	NS	0.015
SV CI	0.133±0.091	0.09±0.033	0.041	0.122	0.103±0.033	NS	NS
Grade I/II/ III/IV varices(%)	0/0/75/25	17.6/47.1/35.3/0	0.002	0/0/70/30	100/0/0/0	0.001	NS
Gastro-oesophageal extension (%)	40	35.3	NS	10	10	NS	NS
Signs of impending rupture(%)	25	0	-	15	0	-	NS
Congestive Gastropathy(%) No/mild/severe	15/15/70	11.8/58.8/29.5	0.008	25/30/45	25/15/60	0.007	NS

Band ligation of esophageal varices is associated with worsening of portal hypertensive gastropathy[14] explaining the change in the congestive gastropathy grade found in both groups of our study. Losartan proved efficacy after 3 months of treatment, there was a significant decrease in splenic volume, SV diameter and SV CI, and statistically non-significant decrease in PV diameter, PV area, PV CI, SV area and SVF was achieved.

There was also a statistically non-significant increase in PV velocity, PVF and SV velocity. This was in agreement with other studies, where Wagatsuma *et al.*[15] reported that the mean PV velocity increased significantly, while the PV CI decreased significantly in cirrhotic patients treated with Losartan for 4 weeks. Also, Hulagu *et al.*[16], found a significant increase in PV velocity and PVF 120 and 240 minutes after 25 mg of Losartan intake. Castaño *et al.*[17] found that Losartan caused a significant decrease in HVPG without changes in portal blood flow and systemic hemodynamics. Regarding the direction of blood flow in the portal vein in our study, it was hepatopedal, hepatofugal or bidirectional before treatment with Losartan while after treatment it was converted to hepatopedal in all patients. Treatment with Losartan increases sodium excretion in cirrhotic patients with and without ascites. The natriuretic effect was more pronounced in cirrhotic patients with ascites than in those without ascites[18]. In our study 23.5% of patients on Losartan showed statistically significant improvement in their ascites grade. Patients tolerated Losartan without significant fall in the mean arterial pressure (MAP) or deterioration of renal function, nearly similar results were found by other studies[19].

Endoscopic band ligation effectively prevents esophageal varices bleeding but it doesn't change the diameter of PV, SMV, SPV or the flow of either the PV or SPV[20]. This is in agreement with the findings in our study where no significant change reported in many studied parameters except for a significant decrease detected in the SV area, SVF and splenic volume, which could be explained by opening of the porto-systemic collaterals. We found that EBVL therapy had some advantages: variceal obliteration was achieved very rapidly, on average of two sessions, with the use of an average of 12 rubber bands. This showed agreement with other studies[21]. Such a rapid eradication may be useful, especially in patients with low compliance, but it is associated with worsening of portal hypertensive gastropathy state[22] and this was seen in 3 patients (15%) of our group in spite of the improvement achieved in their grade of varices and the disappearance of the signs of impending rupture. The frequency of mild complications associated with EVL therapy using multiple ligators was reasonable and consistent with other studies[23]. Superficial ulcers or their residuals were uniformly seen. However, deep ligation-induced ulcers leading to bleeding were not observed. A relatively wide variation in rates of recurrent bleeding has been observed with Endoscopic ligation (10 to

50)[24-27] but no recurrence of the esophageal varices has been seen in our study .This could be explained by the short follow-up period of only three months.

In conclusion:

Both prophylactic EVL & Losartan are effective for primary prevention of variceal bleeding from large sized varices however EVL was associated with worsening of grade of congestive gastropathy and ascites. While Losartan was associated with improved grade of congestive gastropathy and ascites.

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