EFFICACY OF LOSARTAN IN PRIMARY PROPHYLAXIS OF OESOPHAGEAL VARICEAL BLEEDING DUE TO PORTAL HYPERTENSION

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Abstract

This study was designed to evaluate efficacy of Losartan in the primary prevention of oesophageal variceal bleeding and to compare it with that of prophylactic EVL.

It included 40 patients with liver cirrhosis and grade III- IV varices and negative history of variceal bleeding. Both groups were subjected to thorough history taking, clinical examination, laboratory investigations, abdominal ultrasonography, doppler, duplex ultrasonography and upper GI endoscopy. Patients were randomly allocated to receive either EVL or Losartan 50 mg/day and were followed up after three months.

Key Words :

Angiotensin converting enzyme - computerized tomography - Endoscopic Variceal Band Ligation .

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LIST OF ABBREVIATIONS

- **AASLD**: American Association for the Study of Liver Diseases.
- **ACE:** Angiotensin converting enzyme.
- **AT1:** angiotensin type 1.
- **AT2:** angiotensin type 2.
- **AT II**: angiotensin-II.
- **CI**: congestion Index.
- **CSPH**: clinically significant portal hypertension.
- **CT**: computerized tomography.
- **ECM:** extracellular matrix
- **EUS**: endoscopic ultrasonography.
- **ET**: endothelin.
- **EVL:** Endoscopic Variceal Band Ligation
- **GFR:** glomerular filtration rate.
- **GOVs**: gastro-oesophageal varices.
- **HSC:** hepatic stellate cells**.**
- **HTN:** hypertension.
- **HVPG**: hepatic venous pressure gradient.
- **IGVs**: isolated gastric varices.
- **IMN:** isosorbide-5-mononitrate.
- **MAP:** mean arterial pressure.
- **MCP-1**: monocyte chemotactic protein 1.
- **MELD**: model of end stage liver disease.
- **MMP-2**: metalloproteinase 2.
- **MRI**: magnetic resonance imaging.
- **NO**: nitric oxide.
- **NOS**: nitric oxide synthetase.

- **PDGF**: platelet-derived growth factor.
- **PG**: prostaglandin.
- **PHT**: portal hypertension.
- **PV**: portal vein.
- **PVF**: portal vein volume flow.
- **RA:** retinoic acid
- **RAAS**: renin angiotensin activating system.
- **SD**: standard deviation.
- **SMV:** superior mesenteric vein**.**
- **SV:** splenic vein.
- **SVF:** splenic vein volume flow
- **TGF-β:** transforming growth factor β**.**
- **TIMP:** Tissue inhibitor of metalloproteinase.
- **TIPS**: transjugular intrahepatic Portosystemic shunt.
- **TNF α**: tumor necrosis factor α.
- **5-HT:** 5-hydroxytryptamine.

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INTRODUCTION

Portal hypertension (PHT) is a common complication of liver cirrhosis. Cirrhotic patients with PHT develop oesophageal varices and are at very high risk of variceal bleeding (***D'Amico and Luca, 1997***). The incidence of oesophageal varices development is approximately 5% per year in patients with cirrhosis, and the progression from small to large varices occur in 10% to 20% of cases after 1 year. In the 2 years following the first detection of oesophageal varices, the risk of variceal bleeding ranges between 20% to 30% and results in a mortality of 25% to 50% within a week of the first bleeding episode (***D'Amico et al., 2001***). The frequency of bleeding from large varices is 30-53% compared with 5-18% for small varices ***(de Franchis, 2000).***

Primary prophylaxis of oesophageal variceal haemorrhage is an important issue in the management of PHT. Prophylaxis is that which is used to prevent disease ***(Shahi and Sarin, 1998).***

Different treatments have been proposed to prevent first variceal bleeding. Surgical portocaval shunts and endoscopic sclerotherapy significantly reduce first variceal bleeding but at the price of increased side effects and, in some studies, higher mortality. Therefore, they are considered unsuitable. Since PHT reflects elevated splanchnic blood flow and increased intrahepatic vascular resistance, a goal of drug intervention has been to normalize hepatic hemodynamics and reduce vascular resistance. Certain drugs accomplish this by reducing portal blood flow, some by reducing intrahepatic vascular resistance and others by mechanisms that have not been completely clarified ***(Lebrec, 1998).***

Non-selective β-blockers have proved effective in reducing portal pressure by lowering splanchnic blood inflow and are used in primary and secondary prevention of variceal bleeding. However, the mean decrease in portal pressure in response to propranolol is only approximately 15% and one third of cirrhotic

patients do not respond despite adequate blockade **(*Vlachogiannakos et al, 2001).***

Despite the fact that ß-blockers were the main stay for the primary prevention of variceal bleeding, results of EVL in terms of efficacy and safety are promising ***(Bashin and Malhi, 2002).***

During the last decade, increased knowledge of the pathophysiology of PHT has resulted in the use of new pharmacological targets; most importantly for the reduction of intrahepatic resistance, which is now recognized to be due in part to activated stellate cell contraction (myofibroblasts) ***(Sims, 1986).*** Orally active angiotensin II (AT II) receptor antagonists represent a recent therapeutic development in the inhibition of RAAS (renin-angiotensin-aldosterone system) ***(Burnier and Brunner, 2000).*** The RAAS is usually activated in patients with liver cirrhosis and this represents a homeostatic response to counterbalance the vasodilatation, arterial hypotension, and renal hypoperfusion observed in portal hypertension. Plasma renin activity is elevated in cirrhotics and is correlated with the hepatic venous pressure gradient (HVPG)**.** AT II is considered a potential mediator of intrahepatic portal hypertension because its plasma levels are elevated in cirrhosis **(*Vlachogiannakos et al, 2001).*** Infusion of AT-II induces a rise in portal pressure ***(Ballet et al, 1988)***, Enhancement of the adrenergic vasoconstrictor influence on the portal system ***(Goodfriend et al, 1996)***, direct contractile influence on activated stellate cells, and sodium and fluid retention induced by stimulation of aldosterone secretion ***(Pinzani et al, 1992)*** are possible mechanisms that contribute to the portal hypertensive effect of AT II.

Hence, in theory, blockade of the RAAS by angiotensin converting enzyme (ACE) inhibitors/AT-II receptor antagonists should be beneficial for improvement of fluid and salt secretion and reduce portal pressure in cirrhotic patients. ACE inhibitors block the RAAS preventing the conversion of inactive angiotensin I to