

## Can beta - blockers really reduce the progression of small to large varices?

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Variceal bleeding is the most severe complication in patients with cirrhosis and portal hypertension. Any patient with chronic liver disease is at risk of developing esophageal varices as long as a minimal portal pressure threshold of 10-12 mmHg is reached. Once esophageal varices have developed, they tend to increase in size and eventually to bleed. The risk of bleeding in patients with small varices is definitely lower than that in patients with large varices.<sup>1</sup> Progression of small varices to large ones is observed in 4% to 30% of patients with cirrhosis each year.<sup>2</sup> The only significant predictor of variceal enlargement is deterioration of Child Pugh score. Spontaneous regression of esophageal varices is a rare event and related to an improvement in liver function.

Pharmacological therapy with non-selective beta-adrenergic blockers is the established therapy for prevention of variceal hemorrhage. Beta-blockers reduce portal pressure on average 15%-20%. Beta-blockers can also modulate vascular tone in portal-systemic collaterals leading to a selective constriction of collaterals and a decrease in blood flow in gastroesophageal varices. The decrease of portal pressure induced by propranolol is neither dependent on liver function nor the degree of initial portal hypertension or other systemic hemodynamic parameters. However, propranolol does not seem to affect the size of varices, although it reduces variceal pressure.<sup>3</sup>

In 2000, a consensus of experts on portal hypertension suggested that pharmacological prophylaxis with beta-blockers for patients with small varices without red color signs is not recommended, because the risk of bleeding is

low (<10%) and, furthermore, beta-blockers did not seem to reduce significantly the risk of first bleeding.<sup>4</sup> Indeed, three trials examined the effects of beta-blockers on variceal bleeding in patients with cirrhosis and portal hypertension, including a number (20%) of patients with small varices. According to their results, patients receiving beta-blockers had a reduction in variceal bleeding compared to those receiving placebo, without however the difference reaching the level of significance. Thus, the consensus concluded that data regarding the role of beta-blockers in patients with small varices in terms of first bleeding and progression of varices are few and further investigation with large randomized trials is needed.

More recently, two studies have addressed the question of the role of beta-blockers in the progression of esophageal varices.<sup>5,6</sup> In the first study Cales et al studied 206 cirrhotics with small varices or without varices;<sup>5</sup> 102 patients received propranolol and 104 patients placebo. After 2 years of follow up the proportion of patients with large varices was 31% in the propranolol group compared with 14% in the placebo group ( $p < 0.05$ ). The above study however has been seriously criticized; one-third of the patients were lost to follow-up during the study, treatment was given as a fixed dose, without adjustments related to the individual needs, while the incidence rate of large varices in patients receiving placebo was lower than expected at 2 years.<sup>7</sup>

More recently, Merkel et al<sup>6</sup> compared nadolol (83 patients) with placebo (78 patients) with a mean follow-up of 60 months. A significantly lower rate of esophageal varices enlargement in patients randomized to nadolol was observed and a significantly lower probability of variceal bleeding. Survival, however, was not affected by the treatment.

The estimated probability of bleeding within 1 year for Child Pugh grade A patients with large varices and moderate red signs is 24% compared with 20% for Child Pugh C grade patients with small varices and no red signs.<sup>1</sup>

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Thus, some patients with small varices have an important risk of first bleeding. Indeed, only 30% of patients who bleed have “high risk varices”<sup>1</sup> while there is enough evidence supporting the major role of other factors - infection - as a trigger for variceal bleeding.<sup>8</sup> Furthermore, reduction of portal pressure has been related to improvement of liver function, and haemodynamic response to pharmacotherapy has been associated with decreased probability of developing ascites, lower likelihood of developing encephalopathy, reduced requirement for liver transplantation and better survival.

Drug treatment with beta-blockers is inexpensive and early treatment may be favourable from a pharmaco-economic point of view, compared with endoscopic surveillance and treatment when varices become large.<sup>9</sup>

In conclusion, up to date there has been only one study<sup>6</sup> supporting that beta - blockers can reduce the progression of small to large varices in patients with cirrhosis. However, taking into consideration the available data regarding the risk of bleeding in patients with small varices and the efficacy, safety and easy of administration of beta-blockers, we consider that these drugs may be a reasonable therapeutic option, particularly for patients with advanced liver disease, contraindications to endotherapy or living far from endoscopic units. Future well-designed large randomized trials are urgently required in order to explore the importance of pharmacotherapy in patients with cirrhosis and small varices.

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