Published in final edited form as:

Hepatol Int. 2015 July ; 9(3): 337–338. doi:10.1007/s12072-014-9601-1.

Can hypersplenism secondary to portal hypertension be treated by non-selective beta blockers?

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Hypersplenism in chronic liver diseases (CLD) is characterized by splenomegaly and thrombocytopenia. Thrombocytopenia is a contraindication to percutaneous liver biopsy, which is an important procedure for diagnostic work-up of liver disease. In children, the etiologies of CLD are more diverse than in adults, and include congenital, metabolic and infiltrative diseases as well as viral hepatitis. Therefore, liver biopsy is often needed for a definitive diagnosis, which helps to define etiology and therapeutic strategy. Therapies for hypersplenism and thus for thrombocytopenia are limited, however.

In the current issue of *HEPATOLOGY INTERNATIONAL*, Poddar et al.[1] investigated whether propranolol, a long-acting non-selective β -blocker, corrects platelet counts in children with CLD and allows liver biopsy with them. Over a period of 7 years, they recruited 51 children (mean age 11.5 ± 3.0 years) with CLD who needed liver biopsy but could not undergo it because of hypersplenism related thrombocytopenia (platelets $< 100,000/\text{mm}^3$ and/or total leukocyte counts $< 4,000/\text{mm}^3$ with splenomegaly). Patients were administered propranolol (1.5 to 2 mg/kg/day) for 3 to 4 weeks with the goal of achieving platelet counts of $> 100,000/\text{mm}^3$. Propranolol therapy was effective for 32 (62.7%) children and increased mean platelet counts from $57.5 \pm 13.0 \times 10^3/\text{mm}^3$ to $140.7 \pm 43.3 \times 10^3/\text{mm}^3$ ($p = 0.0001$), which permitted liver biopsy in 29 children. Propranolol therapy also reduced spleen size and increased splenic arterial resistance significantly. Therefore, the authors attributed the observed effect of propranolol on increased platelet counts to its vasoconstrictive effect on the splenic artery that would reduce splenic sequestration.

This is the first study that demonstrated the efficacy of propranolol for thrombocytopenia in children, although such an effect was reported in adult cirrhotic patients [2]. The results are impressive, reducing thrombocytopenia in approximately two-thirds of pediatric patients and allowing them to have liver biopsy. Although shunt surgery has been performed to reduce hypersplenism, it is too invasive to be applied to children. Therefore, the development of medical approaches for hypersplenism has been awaited. The approach the authors

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Conflict of Interest: We have no financial interest in or financial conflicts with the subject matter or materials discussed in this manuscript.

employed was based on the pathophysiology of portal hypertension [3]. Portal hypertension is a main cause of hypersplenism in CLD. In portal hypertension, splenic arterial blood flow increases and splenic venous flow into the portal vein is impeded by elevated portal pressure, which cause congestion of intrasplenic blood flow and spleen enlargement. This pooling of blood or platelets in the spleen causes thrombocytopenia. Therefore, the authors attempted to treat thrombocytopenia with propranolol, which has been used for treatment of portal hypertension. This study provides new insight into medical approaches for treatment of hypersplenism.

However, there are several caveats as well. First, the cause of thrombocytopenia and the role of non-selective β -blockers need to be discussed more deeply. Although splenomegaly and thrombocytopenia are commonly observed in cirrhotic patients, they do not always correlate. One study showed that 24% of patients with cirrhosis had splenomegaly while 64% had thrombocytopenia [4]. Splenic sequestration is one cause of thrombocytopenia in CLD. However, other factors also contribute to thrombocytopenia in patients with cirrhosis. These include relatively decreased thrombopoietin synthesis, immune complex-associated platelet clearance, and bone marrow suppression [5]. In addition, a recent pre-clinical study reported that splenomegaly is also related to tissue hyperplasia, enlargement and hyperactivation of the splenic lymphoid tissue, and fibrosis with angiogenesis [6]. Therefore, increasing platelets through the use of a non-selective β -blocker may reflect many changes.

Second, caution is needed for attributing the observed reduction of splenomegaly by propranolol to its vasoconstrictive effect leading to decreased splenic arterial flow. In general, the congestion of splenic venous flow due to elevated portal pressure is also considered as a major cause of splenomegaly. Moreover, the usefulness of transjugular intrahepatic portosystemic shunt (TIPS) and portosystemic shunt operations for recovery of platelet counts has been reported [7]. This indicates the congestion of splenic venous flow as an important cause of splenomegaly. Clinically, non-selective β -blockers have demonstrated to decrease portal venous flow by decreasing splanchnic arterial flow as well as splenic arterial flow. Therefore, the changes in splenic venous congestion and portal venous flow should have been evaluated in this study to more clearly elucidate the path through which propranolol exerted its effect on hypersplenism.

Third and last, the dose and compliance of non-selective β -blockers to children may be cautioned. In this study, only one child showed bronchospasm in response to propranolol treatment. In general, at least 15 – 20% of adult patients show low compliance and side effects with non-selective β -blockers that preclude treatment or require discontinuation [8]. It is reported that propranolol is safe for children, even at high doses [9]. However, no randomized trial has been done for efficacy of non-selective β -blockers in children and to determine appropriate dosages of non-selective β -blockers to children is difficult [10].

As Poddar et al.[1] mention, this study is not a randomized controlled trial. Further studies will warrant the efficacy of non-selective β -blockers for treatment of hypersplenism in children and beyond.

Acknowledgments

We thank Dr. Chuhan Chung for his careful review of the manuscript and helpful suggestions. YI is supported by R01 DK082600 from NIH/NIDDK.

Abbreviations

CLD	chronic liver diseases
TIPS	transjugular intrahepatic portosystemic shunt

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