

# Propranolol for primary and secondary prophylaxis of variceal bleeding in children with cirrhosis

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**SUMMARY:** Ozsoylu Ş, Koçak N, Demir H, Yüce A, Gürakan F, Özen H. Propranolol for primary and secondary prophylaxis of variceal bleeding in children with cirrhosis. Turk J Pediatr 2000; 42: 31-33.

Variceal bleeding due to portal hypertension is a frequent and severe complication of cirrhosis in children as in adults. The prophylactic approach is important for these high mortality bleedings, both for the first and for recurrent attacks. Variceal bleeding/reebleeding rates were evaluated in sixty patients with cirrhosis who received 1-2 mg/kg/day propranolol p.o. for 1-14 years. According to Child-Pugh classification, 33 patients were Class A, 22 Class B, and five Class C. Patients were divided into two groups according to whether they had variceal bleeding before starting propranolol treatment (secondary prevention; 15 patients) or not (primary prevention; 45 patients). Seven (15.6%) of 45 patients experienced bleeding on propranolol therapy in the primary prevention group, while eight (53.3%) of 15 patients bled in the secondary prevention group ( $p < 0.01$ ). Propranolol was found effective in primary and secondary prevention in Class A patients, while it was effective only for primary prevention in Class B and C patients. Propranolol administration is useful for preventing first and recurrent variceal bleeding in Class A cirrhotic patients. In Class B and C cirrhotic patients, it is effective only for preventing the first bleeding episode.

**Key words:** children, cirrhosis, variceal bleeding, propranolol, prophylaxis.

Variceal bleeding due to portal hypertension is a frequent and severe complication of cirrhosis in children as in adults. The prophylactic approach is important for these high mortality bleedings, both for the first and for recurrent attacks<sup>1</sup>. Nonselective  $\beta$ -adrenergic blocker drugs such as propranolol are widely used for this purpose, mostly in adults<sup>2-8</sup>. Data about the effect of  $\beta$ -blockers for prevention of variceal bleeding in cirrhotic children is limited. The aim of this study was to evaluate the effectiveness of propranolol for prevention of variceal hemorrhage in cirrhotic children.

## Material and Methods

Sixty patients with portal hypertension and histopathologically proven cirrhosis, aged between two and a half years and 18 years (mean  $9.9 \pm 3.5$  years), were evaluated in this study. Files of the patients diagnosed between 1982 and 1997 were retrospectively evaluated. All patients were given propranolol at a dose of

1-2 mg/kg/day p.o. bid and the dose was regulated according to a heart rate decrease of 25 percent from the baseline. Patients were divided into two groups: 45 children who had not bled prior to propranolol therapy (primary prevention; PP) and 15 children who had bled before the treatment (secondary prevention; SP). Additionally, patients were evaluated according to Child-Pugh classification<sup>9</sup>. Because we showed that propranolol was effective for lowering portal pressure<sup>4</sup>, it would be unethical to not give propranolol to the control group. Parents as well as older children were strictly instructed to discontinue the drug when bleeding was observed. Patients were examined in the outpatient clinic every three months and hospitalized if they presented with hematemesis or melena. All bleeding episodes were recorded. Neither prophylactic nor therapeutic endoscopic sclerotherapy was used for the patients included in this study. The Sengstaken-Blakemore tube was replaced to stop bleeding when necessary

and blood transfusion(s) was given if indicated. Statistical evaluations were made using Fisher's exact and Kruskal-Wallis tests where appropriate. When comparing groups, patients in Child-Pugh Class B and C were considered together because of the relatively small number of patients in Child-Pugh Class C. A "p" value less than 0.05 was considered as significant.

## Results

The patients were followed for one to 14 years (mean  $5.5 \pm 3.3$ , median 5 years). According to Child-Pugh classification<sup>9</sup>, 33 patients (55%, mean age  $9.8 \pm 3.8$  years) were Child-Pugh Class A, 22 (37%, mean age  $10.0 \pm 3.0$  years) were Child-Pugh Class B and five (8%, mean age  $10.0 \pm 4.3$  years) were Child-Pugh Class C. Mean follow up was  $4.9 \pm 2.3$  years,  $6.8 \pm 4.3$  years, and  $3.4 \pm 1.3$  years, respectively, for the patients in Child-Pugh A, B and C Classes. The mean ages of the patients and mean follow-up duration were not statistically different between the three groups.

Among 45 patients in the PP group, only seven (15.6%) had variceal bleeding under propranolol treatment. Eight out of 15 patients (53.3%) in the SP group experienced recurrent bleeding episode(s) under propranolol treatment ( $p < 0.01$ ).

In Class A patients, two of 28 (7%) patients of the PP group and one of five (20%) patients in the SP group ( $p > 0.05$ ) had a first bleeding episode. These rates were 29 (5/17) and 70 percent (7/10) with Child-Pugh Class B plus C patients ( $p = 0.056$ ) (Table I).

## Discussion

The purpose of drug therapy in portal hypertension is to obtain a sustained decrease in portal pressure. We showed for the first time that propranolol reduces portal pressure in

children with portal hypertension<sup>4</sup> by decreasing portal blood flow through the blockage of  $\beta_1 + \beta_2$  adrenergic receptors<sup>1,10</sup>, obtaining a hepatic venous pressure gradient  $< 12$  mmHg or a decrease of  $> 20$  percent from its baseline level is known to be sufficient for preventing variceal hemorrhage<sup>11</sup>.

It was shown that propranolol was efficient for preventing the first variceal bleeding in Child-Pugh A, B, and C patients<sup>5-7</sup>. In their placebo controlled study, Conn et al.<sup>5</sup> observed an overall bleeding rate of 3.9 percent (82/51) in patients receiving propranolol and of 21.6 percent (11/51) in the control group ( $p = 0.01$ ). When subgroups of Child-Pugh classification were taken into consideration, propranolol was more effective than a placebo in Class B and C patients with cirrhosis ( $p < 0.05$ ), whereas the difference between propranolol and placebo was not significant in patients with Class A cirrhosis. In a multicenter study with 174 patients who had not bled previously<sup>6</sup>, propranolol treatment was compared with vitamin K. The overall bleeding rate was 18.8 percent in the treatment group and 30.3 percent in the control group ( $p < 0.05$ ). A statistically significant result was obtained only in patients with Class A cirrhosis (12% in propranolol group vs 36% in the control group,  $p = 0.01$ ). Pascal et al.<sup>7</sup> compared the efficacy of propranolol for preventing variceal bleeding with a placebo in 230 patients who had no previous bleeding. The bleeding rate in patients in the propranolol group was 17 percent. The cumulative percentage of patients free of bleeding two years after inclusion were 74 percent in the treatment group and 39 percent in the placebo group ( $p < 0.05$ ). They classified their patients as those in good condition and those in poor condition, and the difference was

Table I. Effect of Propranolol in Patients with and without Prior Bleeding According to Child-Pugh Classification

Propranolol therapy	Patients class A		Patients class B+C		Total	
	Bled <sup>a</sup>	Not bled	Bled <sup>b</sup>	Not bled	Bled <sup>c</sup>	Not bled
Primary prevention	3 (7.1)*	26 (92.9)	5 (29.4)	12 (70.6)	7 (15.6)	38 (84.4)
Secondary prevention	1 (20)	4 (80)	7 (70)	3 (30)	8 (53.3)	7 (46.7)
Total	3 (9.1)	30 (80.9)	12 (44.4)	15 (55.6)	15 (33.3)	45 (66.7)

\* Values are percentages.

<sup>a</sup>  $p > 0.05$  (primary prevention vs secondary prevention).

<sup>b</sup>  $p < 0.056$  (primary prevention vs secondary prevention).

<sup>c</sup>  $p < 0.01$  (primary prevention vs secondary prevention).

significant in the patients in poor condition. The study populations of these three studies were adult patients. Additionally, two meta-analyses also showed that propranolol therapy was effective in preventing first bleeding in adult patients with cirrhosis<sup>12,13</sup>. In our study, overall bleeding rate was 15.6 percent in PP patients, which was similar to previous studies<sup>6,7</sup>. It has also been shown that propranolol was more effective for PP than SP.

The efficacy of propranolol of recurrent variceal bleeding is controversial. Lebrech et al.<sup>2</sup> observed recurrent variceal hemorrhage in only one of 38 (3%) patients with compensated cirrhosis (72% Class A). Some other studies deny the efficacy of propranolol in preventing recurrent bleeding. Villeneuve et al.<sup>8</sup> reported recurrent bleeding in 76 percent of 42 patients (89% of whom were Class B and C) receiving the drug. Another study showed a recurrent bleeding rate of 46 percent in similar patients<sup>3</sup>. In our study, while propranolol was effective in SP in Class A patients (20% rebleeding rate), it was inefficient in Class B plus C patients (70% rebleeding rate). In an experimental study, it has been shown that early propranolol administration before collateral circulation development reduced the severity of portal hypertension and portal-systemic shunts in portal vein stenosed rats<sup>14</sup>. Escorcell et al.<sup>15</sup> demonstrated that  $\beta$ -blockers decreased portal pressure more in patients without rather than with varices.

Propranolol seems effective for PP in all cirrhotic patients regardless of the severity of the disease, in other words, both in compensated and decompensated patients, when administered at appropriate doses. However, for SP it is effective in only Child-Pugh Class A patients, but not in the ones with signs of decompensation. For patients who are resistant to propranolol, other options such as endoscopic sclerotherapy, transjugular intrahepatic portosystemic shunt and shunt surgery are available<sup>16</sup>. It is concluded that early propranolol administration is more effective for preventing variceal bleeding in cirrhotic children and that  $\beta$ -blocker therapy started before esophagogastric variceal bleeding would give better results.

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