Management of portal hypertension in children : a retrospective study with longterm follow-up

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Abstract

Objectives : **Data regarding the management of the portal hypertensive haemorrhage in the paediatric patients have yielded conflicting results. The purpose of this study was to evaluate the efficacy of β-blocker (propranolol) alone, sclerotherapy alone and β-blocker + sclerotherapy combination in the management of portal hypertension in the paediatric population.**

Methods : **Medical information was retrieved from the records of 62 children with portal hypertension who were under treatment during at least two years of follow-up period. Data collected included diagnosis, type of portal hypertension, age at initiation of therapy, bleeding episodes before and during therapy.**

Results : **Sixteen of 62 patients were diagnosed as extrahepatic portal hypertension, 46 as intrahepatic portal hypertension. The mean age of study population was 7.6 ± 4.2 years, 45 percent being females. The mean duration of follow-up under therapy was 5.2 ± 2.5 years. Among the patients with intrahepatic portal hypertension, 29 received propranolol + sclerotherapy, 12 received only propranolol and 5 received only sclerotherapy. There was no significant decrease in bleeding episodes during propranolol or sclerotherapy. However patients under propranolol + sclerotherapy, showed significant decrease in bleeding episodes during therapy (23/29 before therapy, 15/29 during therapy, $p < 0.05$). Rebleeding index in patients with IHPH was significantly long in the group treated by propranolol + sclerotherapy ($p = 0.0001$) compared with before therapy. Because the numbers of patients in the groups are small, Kaplan Meier estimation suggest that propranol treatment is more effective. But there isn't significant difference when the results were compared with those of before therapy, except in the combined treatment group**

Conclusion : **The monotherapy is not sufficient for longterm follow-up of portal hypertensive patients. The combination therapy with propranolol + sclerotherapy appears more encouraging in the prevention of portal hypertensive haemorrhage, but this needs to be assessed in randomized trials.** (Acta gastroenterol. belg., **2003**, 66, **213-217**).

Key words : Portal hypertensive haemorrhage, propranolol, sclerotherapy, combination therapy.

Introduction

Data regarding the management of portal hypertensive haemorrhage in the paediatric patients have yielded conflicting results. Beta-blockers, vasopressin, sclerotherapy, endoscopic band ligation and surgical derivations have been known as different methods of treatment for a long time (1-14). Somatostatin and its derivatives, and transjugular intrahepatic portosystemic shunt have also been added to portal hypertension (PH) treatment (7,15,16). Generally, it is reported that propranolol is effective in the prevention of variceal bleeding in children (5,17). However no randomised controlled studies comparing different methods of treatment in children exist. Actually endoscopic band ligation is preferred for the prevention of rebleeding from oesophageal varices (8). The results of the meta-analyses for adults, do not recommande sclerotherapy or rubber band ligation as prophylactic treatments of the first variceal bleeding (18). Medical treatment with β-blockers is considered to be the treatment of choice to prevent the first episode of variceal bleeding in cirrhotics adults (19). In trials comparing sclerotherapy alone with sclerotherapy + β-blockers, the combined treatment is significantly better than sclerotherapy alone in preventing rebleeding in adults (18,19).

The aim of this study is to evaluate the efficacy of β-blocker (propranolol), sclerotherapy and β-blocker + sclerotherapy in the management of PH in a paediatric population.

Materials and methods

In this study, 62 patients with PH who had been under treatment for at least 2 years, were examined retrospectively. Sixteen of 62 patients were diagnosed as extrahepatic portal hypertension (EHPH) and 46 as intrahepatic portal hypertension (IHPH) (Table I).

All patients had evidence of portal hypertension as indicated by oesophageal varices. Doppler-ultrasonography performed for all patients, wasn't sufficient in the differential diagnosis of IHPH and EHPH. All patients except 5 with EHPH underwent liver biopsy. None of the patients with EHPH showed pathological changes in

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Table 1. — **Diagnosis of patients and mode of therapy**

	Diagnosis	Number of patients	Propranolol	Sclerotherapy	Propranolol + Sclerotherapy
EHPH*	Portal venous thrombosis	14	4	4	6
	Splenic venous thrombosis	1	–	–	1
	Splenic venous hypoplasia	1	1	–	–
	Total	16	5	4	7
IHPH**	Cryptogenic cirrhosis	16	4	2	10
	Congenital hepatic fibrosis	9	–	1	8
	Wilson's disease	5	2	–	3
	Chronic hepatitis B	4	2	1	1
	Autoimmune hepatitis	4	2	1	1
	α-1 antitrypsin deficiency	3	–	–	3
	Biliary atresia	2	–	–	2
	Chronic hepatitis C	1	–	–	1
	Idiopathic neonatal hepatitis	1	1	–	–
	Gamma-receptor deficiency	1	1	–	–
	Total	46	12	5	29

* : Extrahepatic portal hypertension.
** : Intrahepatic portal hypertension.

liver biopsy, whereas all patients with IHPH except 9 with congenital hepatic fibrosis, had cirrhosis. Splenoportography was used to differentiate IHPH and EHPH in 13 patients in whom 7 were diagnosed as EHPH. The hepatic venous pressure gradient or splenic pressure wasn't measured.

The mean age of EHPH's population was 5.4 ± 3.4 years, 8 (50 %) being females. The mean age of IHPH's population was 8.4 ± 4.2 years, 20 (43 %) being females. The mean duration of follow-up under therapy was 5.2 ± 2.5 years.

The treatment consisted of β-blocker (propranolol) alone, sclerotherapy alone and β-blocker + sclerotherapy combined (Table I). The type of treatment was chosen according to the severity of the varices. Endoscopic findings were classified according to the North Italian Endoscopic Club index (20) : small varices, grade I, medium-sized varices, grade II, and large varices, grade III. The patients who had grade I-II varices were treated by propranolol, and those who had varices grade III were treated at random by sclerotherapy or combination therapy. Propranolol was given two times per day as 1.0 and 2.0 mg/kg/day. The dosage of propranolol was adjusted to achieve a reduction of 25% in resting heart rate. Sclerotherapy which was used for prophylactic purpose, was repeated at 1 to 4 week intervals, until the mucosa was thickened or the varices were obliterated and the sclerosant (polidocanol 1%) was injected into and around the varice as 5-25 cc/session. The total amount of sclerosant to achieve eradication was indivualized. Sclerotherapy was performed under general anesthesia using Olympus GIF-X20 endoscope and Olympus NM-8L-9L needle. Endoscopic control was performed weekly for 2 or 3 times, then monthly, then in every three months, in every 6 months and finally yearly. Sclerotherapy was regarded successful if there wasn't rebleeding, and the varices were obliterated. This result was obtained generally within 6 months. If sclerotherapy, performed 2 times with 15 days interval was unsuccessful, it was regarded as failure and the Blackmore tube or devascularisation methods were used. In the event of hypersplenism, splenectomy was also performed.

The data were expressed as mean ± SD. Kaplan-Meier estimation was applied to examine the time to the first occurence of bleeding after therapy was initiated. The occurence of bleeding or death due to bleeding from varices were accepted as event. All other data were censored. The Log rank test was used to compare the variation of rebleeding episodes. Rebleeding index for each patient was calculated by dividing the months of follow-up by the number of rebleeding episodes plus 1. P value < 0.05 was considered significant. All statistical tests were performed using SPSS for Windows (SPSS Inc, Chicago, IL, USA) and Microsoft Excell (Realmond, W.A, USA) software. Wilcoxon test was used to compare the rebleeding indexes before and after treatment.

Results

The causes of IHPH were Wilson's disease (5 patients), chronic hepatitis B (4 patients), congenital hepatic fibrosis (9 patients), autoimmune chronic hepatitis (4 patients), chronic hepatitis C (1 patient), α-1 antitrypsin deficiency (3 patients), extrahepatic bile duct atresia (2 patients), idiopathic neonatal hepatitis (1 patient), gamma-receptor deficiency (1 patient) and cryptogenic cirrhosis (16 patients). The causes of EHPH were portal venous thrombosis in 14 patients (3 patients with protein C deficiency, 1 patient with protein S deficiency and 1 patient with antithrombin III deficiency), splenic venous thrombosis in 1 patient and splenic venous hypoplasia in 1 patient.

Seventeen of 62 patients received only propranolol, 9 received only sclerotherapy and 36 received propranolol + sclerotherapy. Twenty-two of 62 patients received

Table II. — **Distrubution of patients receiving treatment**

		Propranolol (*)	Sclerotherapy (*)	Propranolol + Sclerotherapy (*)	Total (*)
Primary Prophylaxis	EHPH**	3 (1)	1 (0)	1 (0)	5 (1)
	IHPH***	10 (1)	1 (0)	6 (1)	17 (2)
	Total	13 (2)	2 (0)	7 (1)	22 (3)
Secondary Prophylaxis	EHPH	2 (1)	3 (3)	6 (4)	11 (8)
	IHPH	2 (1)	4 (3)	23 (14)	29 (18)
	Total	4 (2)	7 (6)	29 (18)	40 (26)

(*) : Number of patients who bled after therapy.
(**) : Extrahepatic portal hypertension.
(***) : Intrahepatic portal hypertension.

treatment as primary prophylaxis, and 40 of 62 patients as secondary prophylaxis (Table II). Because the EHPH group was small, the analyse included the results of IHPH group.

Among the patients with IHPH, 16 had Child A, 27 had Child B, 3 had Child C scores. Eleven of Child A patients were treated with propranolol + sclerotherapy, 3 with propranolol alone, and 2 with sclerotherapy alone. Sixteen of Cild B patients were treated with propranolol + sclerotherapy, 9 with propranolol alone, and 2 with sclerotherapy alone. Two of Child C patients were treated with propranolol + sclerotherapy, and 1 with sclerotherapy alone.

One of 10 patients who received only propranolol and who had experienced no episode of gastrointestinal bleeding before therapy was initiated, had experienced one episode of bleeding after 5 years of therapy. One of 2 patients who had one episode of bleeding before propranolol therapy, had experienced one episode of bleeding after 44 months of therapy. The other patient had no episode of bleeding during 72 months of propranolol therapy.

Three of 4 patients who received only sclerotherapy had experienced at least one episode of bleeding before the therapy was initiated. Only one of 4 patients had no episode of bleeding during 67 months of follow-up. One patient who had no episode of bleeding before sclerotherapy, had also no episode of bleeding during 84 months of follow-up.

Only 6 of 29 patients who received propranolol + sclerotherapy had had no episode of bleeding before therapy. Of the 6 patients who hadn't bled, one bled after 22 months of therapy. On the other hand, 9 patients who had bled before therapy, experienced no episode of bleeding during approximately 43 months of follow-up (24-66 months). Finally 2 of 12 patients in the propranolol group, 3 of 5 in the sclerotherapy group, 15 of 29 in the combined group bled during therapy.

The interval between the beginning of the treatment and the first bleeding was not significantly different by Log Rank test ($p = 0.12$) in the patients with IHPH and, in the three treatment groups (Fig. 1). Despite the suggestion that propranol treatment leads to less rebleeding in view of figure 1, there was no significant decrease in

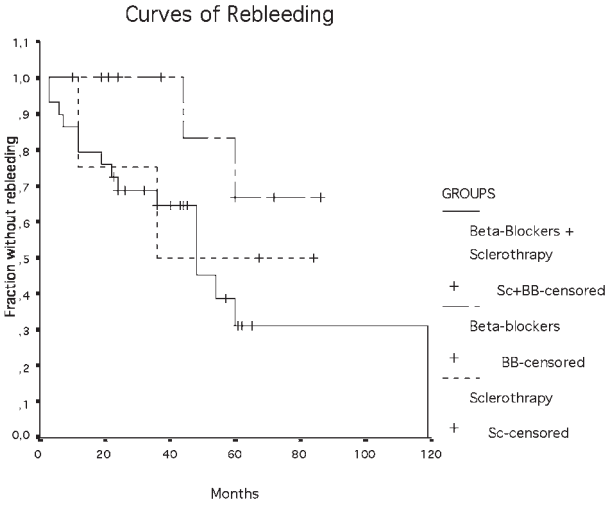

Fig. 1. — Kaplan Meier curves of rebleeding in the patients with IHPH.

bleeding episodes during propranolol therapy or sclerotherapy (2/12 and 4/5 respectively before therapy, 2/12 and 3/5 respectively after therapy). One patient in the propranolol group and 3 patients in the sclerotherapy group who bled after therapy were same patients who have bled before therapy. It is necessary to note that since the number of the patients who had bled before propranolol therapy and the total number of sclerotherapy group are very small, it is difficult to evaluate the efficacy of these treatments. However patients under propranolol + sclerotherapy, showed significant decrease in bleeding episodes during therapy (23/29 before therapy, 15/29 during therapy, $p < 0.05$). Fourteen patients who bled after therapy were same patients who had bled before therapy, one patient who hadn't bled before therapy, bled after therapy. Rebleeding index in patients with IHPH was significantly long in the group treated by propranolol + sclerotherapy ($p = 0.0001$) compared with before therapy (Table III).

The time between the initiation of therapy and the first bleeding episode was 4.3 ± 0.6, 1.6 ± 0.9 and 2.6 ± 2.4 years in the groups who received only propranolol, only sclerotherapy or propranolol + sclerotherapy, respectively.

Table III. — **Rebleeding indexes in the patients with IHPH**

	Before therapy	After therapy	P
Propranolol	0.22 ± 0.3	0.044 ± 0.033	0.22
Sclerotherapy	0.91± 1.2	0.073 ± 0.03	0.14
Propranolol + Sclerotherapy	0.36 ± 0.42	0.040 ± 0.03	0.0001

Before therapy, among 29 patients with IHPH, 5 had had portal hypertensive gastropathy. During treatment, in 4 patients recurrent oesophageal varices and in 7 patients (in 2 patients both recurrent varices and portal hypertensive gastropathy) portal hypertensive gastropathy developed. A mean of 3 sessions of sclerotherapy were required to achieve variceal obliteration.

During follow-up, four patients (2 cryptogenic cirrhosis, 1 autoimmune hepatitis, 1 α-1 antitrypsin deficiency) died because of massive variceal bleeding (2 of them had received sclerotherapy and 2 had received propranolol + sclerotherapy), and two patients (1 chronic hepatitis B, 1 biliary atresia) who had received propranolol + sclerotherapy died during the postoperative period of liver transplantation. The last two died 2 days and 18 days after liver transplantation respectively (because of acute rejection and mycotic sepsis).

Discussion

The opinion considering the preponderance of EHPH in the paediatric age group has changed in time. In the report of Goh and Myers (21) EHPH being dominant (71%) between 1948-1971, the spectrum of PH was changed to IHPH (62%) between 1971-1991. In our study also, IHPH constituted the majority of portal hypertensive patients. The reason why IHPH is becoming more prevalent is not clear (22). Decrease in the use of umbilical catheter may be one of the causes. The majority of our extrahepatic portal hypertensive patients had portal vein thrombosis, like stated in the literature (1,23). Cryptogenic cirrhosis with a rate of 28%, predominated in the aetiology of IHPH, and supported the other authors' results (1,23,24).

Variceal bleeding is a major, potentially life-threatening clinical complication of PH that require urgent medical intervention (25). Although advances in the emergency management, variceal haemorrhage still remains a leading cause of morbidity and mortality in these patients (26). The estimated risk of a first variceal bleeding episode in patients with PH vary from 27% to 48% (27). In adults with cirrhosis the initial bleeding carries a mortality of 39% to 54%, and up to two thirds of those who survive experience rebleeding (28,29). In adults, controlled studies have shown that endoscopic variceal ligation is superior to endoscopic injection sclerotherapy in terms of safety as well as efficacy in controlling active bleeding and preventing rebleeding (18). Non-selective β-blocker have also proven to be effective in the prevention of variceal rebleeding (19). Recently, it is reported that a combination of endoscopic variceal ligation, β-blocker and sucralfat is better than endoscopic variceal ligation alone in adults (8). In children, there are also studies reporting that endoscopic variceal ligation is effective and safe in children, even in very young ones (9,11,30,31). Very recently, Zargar *et al.* (11) reported that endoscopic variceal ligation in children achieves a lower rebleeding rate and fewer complications compared with sclerotherapy. There are no studies comparing different methods of treatment preventing variceal bleeding in the paediatric population. Further studies are necessary to compare the efficacy of the combination of endoscopic variceal ligation + β-blocker versus endoscopic variceal ligation alone.

In the study of Shashidhar *et al.* (17), it is reported that the use of propranolol in the prevention of variceal bleeding is effective. In this retrospective, nonrandomized, open trial, 21 children aged from 9 months to 18 years received propranolol in variable dose schedule. Fourteen of the 21 children did not experience a bleeding episode while receiving propranolol. Bleeding episodes occured in 19% of the patients with cirrhosis who were adequately treated. Also, Özsoylu *et al.* (5) reported that propranolol was specially effective in primary and secondary prevention in Child A patients, while it was effective only for primary prevention in Child B and C patients. Our study being retrospective and nonrandomized, despite the same ratio of bleeding before and after therapy, supported the efficacy of propranolol in the primary prophylaxis (9 of 10 patients) as it is stated in the literature (5,17). As there were patients who bled after 5 years of propranolol therapy, it seems that prospective, multicenter, longterm studies need to be performed.

Sclerotherapy is successful in more than 85% of the patients, but rebleeding occurs in up to 50% of patients ; most are controlled with repeated treatments (22). In our study there was no significant decrease in rebleeding episodes after sclerotherapy (3/5 patients). This was probably due to developed varices (2 patients) and hypertensive gastropathy (3 patients) after sclerotherapy (32-34). But in our study the number of patients in the sclerotherapy group is small in both primary and secondary prophylaxis groups (1 and 4 respectively). This distribution limits the interpretation in regard to efficacy. Generally endoscopic prophylactic sclerotherapy is restricted to adult patients and has led to conflicting results (35,36). However Goncalves *et al.* (34) demonstrated in a prospective study that prophylactic sclerotherapy reduced the incidence of bleeding from oesophageal varices that were eradicated in 94% of cases. Our retrospective study supported the use of prophylactic sclerotherapy, because none of the patients bled in the sclerotherapy group (0/1) and only one of 6 patients bled in the combined therapy group.

Because the numbers of patients in the groups are small, Kaplan Meier curves suggest that propranol treatment is more effective. But there isn't significant

difference when the results were compared with those of before therapy, except in the combined treatment group. Moreover, the patients receiving propranol are those who had lower grade of varices, so they had lower risk of bleeding. Despite the use of combination therapy in the patients who had more severe varices, a significant decrease was observed in the bleeding episodes after initiation of the therapy. Further studies comparing different methodes of treatments in the groups with the same grade of varices may provide better results.

In conclusion, monotherapy was not sufficient for longterm follow-up of portal hypertensive patients, but the combination therapy with propranolol + sclerotherapy appeared more encouraging in the prevention of variceal haemorrhage in children, but this needs to be assessed in randomized trials.

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