

# EVALUATION OF PRIMARY PROPHYLAXIS WITH PROPRANOLOL AND ELASTIC BAND LIGATION IN VARICEAL BLEEDING IN CIRRHOTIC CHILDREN AND ADOLESCENTS

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**ABSTRACT - Background** - The efficacy of nonselective  $\beta$ -blocker and endoscopic procedures, such as endoscopic variceal ligation, as primary prophylaxis of variceal hemorrhage in cirrhotic adults was demonstrated by numerous controlled trials, but in pediatric population, few are the number of studies. **Objective** - The objective of this study is to evaluate the primary prophylaxis with  $\beta$ -blocker in cirrhotic children and adolescents with portal hypertension. **Methods** - This is a cohort study encompassing 26 cirrhotic patients.  $\beta$ -blocker prophylaxis was performed with propranolol. When contraindicated the use of  $\beta$ -blocker, or if side effects presents, the patients were referred to endoscopic therapy with band ligation. Patients were evaluated by endoscopy, and those who had varicose veins of medium and large caliber or reddish spots, regardless of the caliber of varices, received primary prophylaxis. **Results** - Of the 26 patients evaluated, 9 (34.6%) had contraindications to the use of propranolol and were referred for endoscopic prophylaxis. Six (35.3%) of the 17 patients who received  $\beta$ -blocker (propranolol), had bled after a median follow-up time of 1.9 years.  $\beta$ -blockage dosage varied from 1 mg/kg/day to 3.1 mg/kg/day and seven (41.2%) patients had the propranolol suspended due to fail of the  $\beta$ -blockage or adverse effects, such as drowsiness, bronchospasm and hypotension. Patients who received endoscopic prophylaxis (elastic bandage) had no bleeding during the follow-up period. **Conclusion** - All of the patients that had upper gastrointestinal bleeding in this study were under propranolol prophylaxis. The use of propranolol showed a high number of contraindications and side effects, requiring referral to endoscopic prophylaxis. The endoscopic prophylaxis was effective in reducing episodes of bleeding. **HEADINGS** - Liver cirrhosis. Esophageal and gastric varices, therapy. Disease prevention. Propranolol. Gastrointestinal endoscopy, rehabilitation. Child. Adolescent.

## INTRODUCTION

Portal hypertension is a common complication of chronic liver disease in children<sup>(3)</sup>. In cirrhosis, portal pressure initially elevates as a consequence of an increased resistance to flow mostly due to an architectural distortion of the liver secondary to fibrous tissue and regenerative nodules<sup>(6,11,16)</sup>. In addition, intrahepatic increased vascular tone, small vessel portal thrombosis, and splanchnic arteriolar dilatation exacerbate portal hypertension<sup>(3,6,11)</sup>.

Varices are portosystemic collaterals formed as a result of elevated hepatic venous pressure gradient, which dilates preexisting vascular channels<sup>(11,16)</sup>.

Variceal bleeding occurs when variceal wall tension is increased beyond the maximum tolerable threshold, as a result of increased variceal vein diameter, decreased wall thickness, and increased intraluminal pressure<sup>(11)</sup>. In some pediatric hepatology referral centers, more than 50% of cirrhotic children have varices<sup>(9,11,16)</sup>.

Endoscopy is the reference standard for diagnosis of esophageal varices. Adults who are likely to have portal hypertension and to be at risk of esophageal varices should be screened by endoscopy, and who have varicose veins of medium and large caliber or reddish spots, regardless of the caliber of varices have been recommended primary prophylaxis<sup>(18)</sup>.

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Primary prophylaxis is intended to prevent the first episode of variceal bleeding in an individual who has varices<sup>(9)</sup>. There is no consensus on whether primary prophylaxis is indicated for cirrhotic children<sup>(3,6,11)</sup>. The efficacy of nonselective  $\beta$ -blocker and endoscopic procedures, such as endoscopic variceal ligation (EVL), as primary prophylaxis of variceal hemorrhage in cirrhotic adults was demonstrated by numerous controlled trials<sup>(6,7,14)</sup>. Primary prophylaxis is also commonly used in cirrhotic children, despite the lack of pediatric data, based on extrapolations of the adult studies to children<sup>(3,11)</sup>.

The objective of this study is to evaluate the primary prophylaxis with  $\beta$ -blocker in cirrhotic children and adolescents with portal hypertension.

## METHODS

This is a cohort study encompassing 26 cirrhotic patients who underwent primary prophylaxis for upper gastrointestinal bleeding at the Hospital das Clínicas of the Federal University of Minas Gerais (HC/UFMG), Brazil, between 2004 and 2014. The endoscopic findings were classified based on the "General Rules for Recording Endoscopic Findings of Esophagogastric Varices (2nd edition)" by Japanese Research Society for Portal Hypertension<sup>(20)</sup>. Patients were evaluated by endoscopy, and those who had varicose veins of medium and large caliber or reddish spots, regardless of the caliber of varices, received primary prophylaxis.

$\beta$ -blocker prophylaxis was performed with propranolol, 1 mg/kg/day initially q8hr, titrated to reduce the basal heart rate by 25% and not exceeding 5 mg/kg/day or 320 mg/day, and were evaluated every month until this value was reached and every 3 months thereafter. EVL was performed in patients with contraindications to  $\beta$ -blockers or those who discontinued treatment due to adverse effects or poor compliance. The endoscopic procedure, elastic bandage, was done in accordance to the Protocol of the Service. The elastic bandage was performed using a multi band ligator (Wilson-Cook Medical, USA), under general anesthesia performed by pediatric anesthesiologist. The ligation started near the gastroesophageal junction, heading 5 cm cephalically. In each session, all the eligible varices found were connected using elastic rings. The procedure was repeated every 3 weeks until eradication of the varices. Follow-up examinations were performed every 3 months during the first 6 months, then after 6 months and, finally, annually, if no varices were found.

Data such as gender, age at first endoscopy and when prophylaxis was started, cause of cirrhosis, laboratory and clinical data, type of prophylaxis (propranolol or endoscopic), follow-up time and date of gastrointestinal bleeding were searched on the patients' medical records.

The patient database was developed and analyzed using the program SPSS 17. Continuous variables with normal distribution were expressed as mean and standard deviation (SD)

and continuous variables without normal distribution were expressed as median and 25%-75% interquartile range (IQ 25-75%).

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais, number 254/04.

## RESULTS

Of the 26 patients evaluated, 10 (38.4%) were male and had a median of 7.9 years old (25%-3 / 75%-13) at the start of primary prophylaxis. They were followed for 2.3 years (25%-1.3 / 75%-3.3).

Seventeen started prophylaxis with propranolol with a median of 7.6 years old ( $P25\%=3.5$  /  $P75\%=13.2$ ) at the start of therapy and had a median follow-up time of 2.7 years ( $P25\%=1.2$  /  $P75\%=3.5$ ), five with autoimmune hepatitis and seven with biliary atresia. Six (35.3%) patients of seventeen bleed, with a median time of 1.9 years ( $P25\%=0.6$  /  $P75\%=2.9$ ) of propranolol use. Three (17.6%) of the six patients that bled died during the follow-up period due to acute bleeding when they used propranolol. They died after a median of 2.9 years ( $P25\%=1.65$  /  $P75\%=3.15$ ) of propranolol use and with a median of 6.9 years old ( $P25\%=4.2$  /  $P75\%=7.5$ ). Four (66.6%) of the six patients that bled had biliary atresia.

In seven (41.2%) patients the propranolol prophylaxis were suspended during the study, with a median of 8.6 years old (25%-6.4 / 75%-13.1) at the time of suspension, and median of 1.2 years ( $P25\%=0.85$  /  $P75\%=2.2$ ) of propranolol use, three by not achieved the  $\beta$ -blockage and four by side effects, such as drowsiness, bronchospasm and hypotension. Data of patients who underwent beta blocker prophylaxis are shown in Table 1.

Patients who underwent endoscopic prophylaxis with elastic band ligation are shown in Table 2. Thirteen patients were included in this group, nine with initial contraindications to propranolol use and four that were referred from betablocker group by side effects or betablockage failure. They had a median of 9 years old ( $P25\%=2.4$  /  $P75\%=12.3$ ) and had a median follow-up time of 2.2 years ( $P25\%=1.9$  /  $P75\%=2.6$ ). In this group, seven had biliary atresia and two autoimmune hepatitis. No bleeding episodes and no deaths in this group were observed.

Table 3 and Figure 1 shows the summary of results.

In summary, 17 patients started primary prophylaxis with beta blocker, nine were male gender. Biliary atresia and autoimmune hepatitis were the most prevalent diagnoses, with seven and three cases respectively. They were followed for median of 2.7 years. Six patients had upper gastrointestinal bleeding after a median time of 1.9 years and three died.

In the endoscopic procedure group, of the 13 patients, 9 were female gender, and biliary atresia was the most prevalent diagnoses in seven cases. The median follow-up time of this group was 2.2 years, and no patient had bleeding.

The Figure 1 summarize the results and the global evaluation of the study.

**TABLE 1.** Description of 17 children and adolescents with cirrhosis who underwent propranolol prophylaxis

#	Gender	Diagnosis	Grade of Varices at start of therapy	Age at start of therapy (yr)	Therapy	Follow-up (yr)
1 *	M	BA	Medium	13.6	Suspended after 2.7 years (failed $\beta$ -blockage)	2.7
2 *	F	BA	Medium	6.9	Suspended after 1.7 years (unresponsive to a dose of 4.6 mg/kg)	1.7
3	M	Others	Medium	4.7	$\beta$ -blockage achieved at 3.1 mg/kg	6
4	M	BA	Large	13.8	$\beta$ -blockage achieved at 1.0 mg/kg	3.5
5	F	Others	Medium	5.1	$\beta$ -blockage achieved at 2.0 mg/kg	Bleed and died after 2.9
6 *	M	PSC	Medium	7.6	Suspended after 6 months (drowsiness)	0.5
7	F	BA	Large	2.9	Suspended after 2.4 months (bronchospasm)	Bleed after 0.4
8	F	Others	Medium	3.5	Suspended after 1.2 years (hypotension and convulsion)	Bleed and died after 3.4
9	M	AH and AC	Medium	13.2	$\beta$ -blockage achieved at 1.0 mg/kg	4.8
10	F	BA	Large	2.0	$\beta$ -blockage achieved at 1.0 mg/kg	Bleed after 2.8
11	F	AH and AC	Medium	15.0	$\beta$ -blockage achieved at 1.9 mg/kg	3.8
12	M	AH	Large	16.9	$\beta$ -blockage achieved at 1.2 mg/kg	2.2
13	F	ChC	Large	8.2	$\beta$ -blockage achieved at 1.2 mg/kg	2.3
14	M	BA	Large	1.2	$\beta$ -blockage achieved at 1.0 mg/kg	Bleed after 1.0
15	F	AH	Medium	10.8	Suspended after 3 years (drowsiness)	3.7
16	M	BA	Large	1.1	$\beta$ -blockage achieved at 1.0 mg/kg	Bleed and died after 0.4
17 *	M	AH and AC	Large	11.2	Suspended after 1.2 years (failed $\beta$ -blockage)	1.2

BA: biliary atresia; AH: autoimmune hepatitis; PSC: primary sclerosing cholangitis; ChC: choledocal cyst; CC: cryptogenic cirrhosis; AC: autoimmune cholangitis; GV: gastric varices. M: male; F: female. \* Went to EVL after using  $\beta$ -blocker.

**TABLE 2.** Description of 13 children and adolescents with cirrhosis who underwent endoscopic prophylaxis

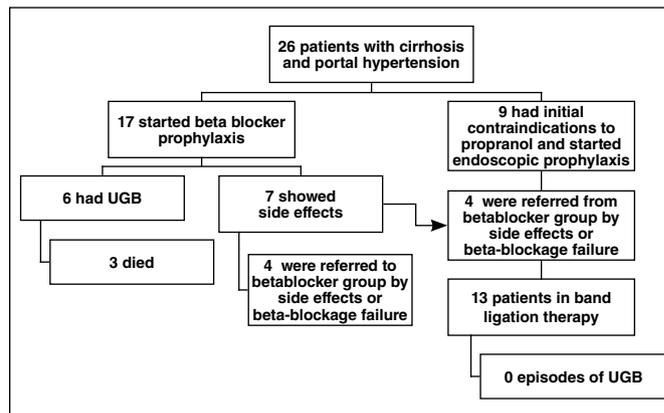
#	Gender	Diagnosis	Grade of Varices at start of therapy	Age at start of therapy (yr)	Follow-up (yr)
1 *	M	BA	Medium	13.8	6.7
18	F	AH and AC	Medium and GV	4.9	10.3
2 *	F	BA	Large	9.1	0.2
6 *	M	PSC	Medium	9.0	2.1
19	F	CC	Large	10.3	2.5
20	F	CC	Large	16.0	2.2
21	M	BA	Large and GV	14.0	1.7
22	F	BA	Large	1.2	2.3
23	F	BA	Large	3.2	2.0
24	F	BA	Large	2.4	0.2
25	F	BA	Medium	2.0	3.0
26	F	CC	Large	2.1	0.3
17 *	M	AH and AC	Large	12.3	2.2

BA: biliary atresia; AH: autoimmune hepatitis; PSC: primary sclerosing cholangitis; CC: cryptogenic cirrhosis; AC: autoimmune cholangitis; GV: gastric varices. M: male; F: female. \* Went to EVL after using  $\beta$ -blocker.

**TABLE 3.** Summary of primary prophylaxis

Therapy	N	Gender	Diagnosis	Follow-up (yr)	Bleeding
$\beta$ -blocker	17	8 F 9 M	7 BA 3 AH and AC 3 others 2 AH 1 PSC 1 ChC	2.7 (median) (p25% 1.2 / p75% = 3.5)	6, after median of 1.9yr, and 3 deaths
EVL	13	9 F 4 M	7 BA 3 CC 1 PSC 2 AH and AC	2.2 (median) (p25% 1.7 / p75% 3.5)	0

BA: biliary atresia; AH: autoimmune hepatitis; PSC: primary sclerosing cholangitis; ChC: choledocal cyst; CC: cryptogenic cirrhosis; AC: autoimmune cholangitis. F: female; M: male.



**FIGURE 1.** Summary and global evaluation of primary prophylaxis. UGB: upper gastrointestinal bleeding.

## DISCUSSION

Considering the limited experience of primary prophylaxis with beta blocker in children and adolescents with cirrhosis and portal hypertension, and the need for greater knowledge about the indications in pediatric patients, this study had the initial objective to evaluate the use of propranolol in pediatric patients. One of its limitations is the small sample size, as well as other few studies present in the pediatric literature.

The primary objective of pharmacologic therapy for variceal bleeding is to reduce portal pressure and, consequently, intravariceal pressure<sup>(16)</sup>. Nonselective  $\beta$ -blockers, such as propranolol, can decrease portal flow, intrahepatic vasoconstriction, and the splanchnic blood flow<sup>(16)</sup>. In adults, a dose reducing heart rate by 25% decreases the bleeding rate in cirrhosis<sup>(3)</sup>. In children, the evaluation of heart rate in rest is problematic and the range of drug dosage to reduce it by 25% is very wide, making achievement of proper dosage impractical and time consuming<sup>(3)</sup>. Other issues regarding the use of  $\beta$ -blockers are the prolonged need for therapy, the risk of bleeding after cessation and the frequent side effects and contraindications<sup>(13)</sup>.

In adults, the effectiveness of endoscopic primary prophylaxis and drug primary prophylaxis are similar, with reduced reporting rates of bleeding and mortality<sup>(7,14)</sup>.

The first study of propranolol in children was published in 1985. The authors demonstrated a decrease portal vein pressure after drug administration on 13 children. However, there was no follow-up of patients or the control group, in order to determine the risk of gastrointestinal bleeding. The authors suggest that the drug may be useful in portal hypertension compensated or decompensated and emphasize the good tolerance and low incidence of side effects<sup>(12)</sup>.

Samanta et al.<sup>(13)</sup> evaluated 41 patients, most of them with small caliber esophagus varices according the criteria of Conn<sup>(2)</sup>, and had great results, with a low rate of bleeding. The adverse effects have not been addressed, only being cited the absence of hypotension in patients during follow-up. Shashidhar et al. reported the experience with the use of propranolol in 21 children and adolescents with portal hypertension, 19 patients with cirrhosis and two with portal vein obstruction. In this retrospective, non-randomized, uncontrolled study, children aged 9 months to 18 years received propranolol in a dose of 0.6 to 7.0 mg/kg/day, in two to four times a day. The study was not homogeneous, as evaluated patients undergoing primary and secondary prophylaxis. The measurement of venous portal gradient was not obtained. Despite the limitations, 14 of 21 children showed no episodes of upper gastrointestinal bleeding while receiving medication. Of the seven patients who bled two did not adhere to treatment and two did not show reduction of at least 25% of heart rate. Excluding these patients, episodes of upper gastrointestinal bleeding occurred in 19% of cirrhotic patients adequately treated. The beneficial impact of this prophylactic measure was not adequately demonstrated due to the absence of the control group and randomization<sup>(17)</sup>. They reported side effects such as urticarial rash, dizziness, bradycardia, hypotension and depression in 33% of patients, without interruption of treatment in any case.

In the present study,  $\beta$ -blockage dosage varied from 1 mg/kg/day to 3.1 mg/kg/day and seven patients (41.2%) had the propranolol suspended due to the fail of  $\beta$ -blockage or adverse effects, such as drowsiness, bronchospasm and hypotension. The dosage of propranolol used at the pediatric studies were 1 mg/kg/day to 2 mg/kg/day, orally<sup>(13,17)</sup>. Six (35.3%) of the 17 patients who received  $\beta$ -blocker had bled after a median follow-up time of 1.9 years (0.6-2.9), and 3 (17.6%) died due to bleeding. The high rates of side effects such as those presented in this study and the difficulty in reaching the beta blockade are hindering the use of propranolol in pediatric patients, leading to studies with low numbers of patients. The bleeding rate of 35.3% observed in this study is similar to that of 31.5% observed in the study of Shashidhar et al.<sup>(17)</sup>. Samanta et al.<sup>(13)</sup> reported a lower bleeding rate, that was 4.9%. Only these studies have evaluated the bleeding rate of children receiving primary prophylaxis with  $\beta$ -blocker.

The Expert Pediatric Opinion on the Report of the Baveno V Consensus Workshop on Methodology of Diagnosis and Therapy in Portal Hypertension states all patients who have medium or large caliber varicose veins, or red spots on varicose veins, regardless of the caliber of esophageal varices must be evaluated to receive primary prophylaxis, preferably by the method of EVL, and that the use of beta blockers as a way to primary prophylaxis should be restricted to research centers<sup>(18)</sup>. There are few studies in the pediatric population, in general case series, with small numbers of patients, similar to our study<sup>(1,13,17,15)</sup>.

EVL can prevent variceal bleeding through rubber band ligation of the variceal vessel, causing a mechanical strangulation<sup>(9)</sup>. EVL is often not a practical option for small children because it is difficult to insert the device-attached endoscopic probe into their small esophageal lumen<sup>(10)</sup>. The usefulness of primary prophylaxis of bleeding by endoscopic obliteration in children is still unproven<sup>(3)</sup>. A randomized controlled trial suggested that sclerotherapy is effective as primary prophylaxis for variceal bleeding in children; however, the study showed an increased incidence of congestive hypertensive gastropathy and gastric bleeding after the procedure<sup>(4,8)</sup>. Sclerotherapy has not been indicated for primary prophylaxis in children, due to its unfavorable adverse effect profile, and it recommends the use of EVL as a way to primary prophylaxis<sup>(18,19)</sup>. In this study, none of the 13 patients who received EVL had bled, showcasing be an effective and safe method for the pediatric age group.

Bleeding occurs in approximately 30% of patients with varices<sup>(16)</sup>. In this study, despite the onset of primary prophylaxis six (23.1%) out of 26 bled. A bleeding episode from esophageal varices is associated with significant adverse sequelae, such as blood transfusion and intensive care<sup>(11)</sup>. A mortality ratio of 19% was reported among North American children with liver diseases of various etiologies, within 35 days of variceal bleeding episodes<sup>(5)</sup>. The mortality of cirrhotic children at the time of first bleeding episode is estimated to be 5%-15%<sup>(3)</sup>. Three (50%) of the six patients that bled in this series end up dying.

In conclusion, all of the six patients that had upper gastrointestinal bleeding were under propranolol prophylaxis. The high suspension rate (41.2%) due to adverse effects or poor compliance in patients using propranolol makes it impracticable to be used as primary prophylaxis, despite its potential, but not proved, benefits. The endoscopic primary prophylaxis seemed to be safe and effective, since none of the patients who underwent EVL bled or had significant complications during the follow-up.

It's a small case series, with a few number of patients, and aimed to be a larger study. Given the side effects, low adherence and bleeding rate in the propranolol group,

we suspended the routine use of propranolol for primary prophylaxis at our institution and all electable children receive EVL.

However, more studies are needed to show the real efficacy and safety of propranolol and endoscopic prophylaxis for variceal bleeding in cirrhotic children.

#### Authors' contributions

Pimenta JR: implementation of research, writing and statistical analysis. Ferreira AR: implementation of research, writing and statistical analysis. Bittencourt PFS: search execution. Resende CB: data collection, writing and analysis statistics. Fagundes EDT: search execution. Silva IML: data collection.

Pimenta JR, Ferreira AR, Bittencourt PFS, Resende CB, Fagundes EDT, Silva IML. Avaliação da profilaxia primária em crianças e adolescentes cirróticos com propranolol e ligadura elástica. *Arq Gastroenterol.* 2016;53(4):257-61.

**RESUMO - Contexto** - A eficácia dos beta-bloqueadores e de procedimentos endoscópicos como a ligadura elástica endoscópica para profilaxia primária de ruptura de varizes de esôfago em adultos cirróticos já foram demonstrados por inúmeros ensaios clínicos na população adulta, porém poucos são os estudos envolvendo a faixa etária pediátrica. **Objetivo** - Avaliar a profilaxia primária com  $\beta$ -bloqueador em crianças e adolescentes cirróticos com hipertensão porta. **Métodos** - Estudo de coorte envolvendo 26 pacientes cirróticos. O propranolol foi o  $\beta$ -bloqueador utilizado para a profilaxia. Quando contraindicado o uso de  $\beta$ -bloqueador, ou se efeitos colaterais presentes, os pacientes eram encaminhados para profilaxia endoscópica com ligadura elástica. Os pacientes foram avaliados por endoscopia, e naqueles que foram observadas varizes de médio e/ou grosso calibre ou presença de manchas avermelhadas nas varizes, independentemente do calibre das varizes, a profilaxia primária foi indicada. **Resultados** - Dos 26 pacientes avaliados, 9 (34,6%) tinham contraindicações para o uso de propranolol e foram encaminhados para a profilaxia endoscópica. Seis (35,3%) dos 17 pacientes que receberam  $\beta$ -bloqueador (propranolol) apresentaram sangramento após mediana de tempo de acompanhamento de 1,9 anos. A dose de  $\beta$ -bloqueio variou de 1 mg/kg/dia a 3,1mg/kg/dia e em sete (41,2%) pacientes o propranolol foi suspenso por falha em atingir  $\beta$ -bloqueio ou presença de efeitos adversos, tais como sonolência, broncoespasmo e hipotensão. No grupo de pacientes que receberam a profilaxia endoscópica (ligadura elástica) não foi observado nenhum episódio de hemorragia digestiva alta durante o período de acompanhamento. **Conclusão** - Todos os pacientes que apresentaram hemorragia digestiva alta no presente estudo estavam recebendo profilaxia com propranolol. Foi observado, ainda, elevado número de contraindicações e efeitos colaterais, com consequente encaminhamento para profilaxia endoscópica. A profilaxia endoscópica foi eficaz na redução de episódios de hemorragia digestiva alta.

**DESCRITORES** - Cirrose hepática. Varizes esofágicas e gástricas, terapia. Prevenção de doenças. Propranolol. Endoscopia gastrointestinal, reabilitação. Crianças. Adolescente.

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