

Octreotide for acute gastrointestinal bleeding secondary to portal hypertension in pediatric patients: experience of a tertiary center

Uso de octreotida na hemorragia digestiva alta secundária à hipertensão portal em pacientes pediátricos: experiência de um serviço terciário

Uso de octreotide en la hemorragia digestiva alta secundaria a hipertensión portal en pacientes pediátricos: experiencia de un servicio terciario

Daniela Gois Meneses¹, Elizete Aparecida L. C. Pinto², Adriana Maria A. de Tommaso²

ABSTRACT

Objective: To describe clinical data of children and adolescents with portal hypertension, during with and without liver cirrhosis, treated with octreotide during episodes of acute upper gastrointestinal bleeding.

Methods: Retrospective and descriptive study of 26 episodes of gastrointestinal bleeding in 17 patients (mean age: 8.6 years; range: seven months to 18.9 years) assisted at a tertiary university hospital from 1996 to 2006. Portal hypertension diagnosis was based on ultrasonography. Liver cirrhosis was confirmed by histology and hepatic function was classified according the Child-Pugh score.

Results: Portal hypertension etiology was extra-hepatic portal vein obstruction in 11/17 (65%) patients and cirrhosis in 6/17 (35%). Bleeding was controlled in 14/17 (82%) patients. Octreotide infusion requirement was similar in cirrhotic and non-cirrhotic patients, but the decline in hemoglobin levels and the requirement of blood transfusions were greater but not significant in cirrhotic patients. The patients' responses were similar regardless of drug infusion strategy. Whether it included a loading dose or not. Treatment failure was observed mainly among cirrhotic patients (33%). Hyperglycemia was the only side effect detected during octreotide infusion.

Conclusions: Octreotide administration in children and adolescents with digestive bleeding due to portal hyper-

tension was safe and effective in order to control the acute episode of bleeding, regardless of the etiology of portal hypertension and infusion strategy.

Key-words: octreotide; gastrointestinal bleeding; hypertension, portal; child; adolescent.

RESUMO

Objetivo: Descrever a evolução clínica dos episódios de hemorragia digestiva em crianças portadoras de hipertensão portal, com e sem cirrose, tratadas com octreotida.

Métodos: Estudo retrospectivo e descritivo de 26 episódios de sangramento digestivo em 17 pacientes (média de idade: 8,6 anos; variação: sete meses a 18,9 anos), no período de 1996 a 2006, num hospital terciário universitário. O diagnóstico de hipertensão portal foi estabelecido por ultrassonografia e a cirrose foi confirmada pela histologia e classificada quanto à gravidade pelo escore de Child-Pugh.

Resultados: As causas da hipertensão portal foram: obstrução extra-hepática da veia porta em 11/17 casos (65%) e cirrose hepática em 6/17 (35%). O sangramento foi controlado em 14/17 pacientes (82%). O tempo de infusão da droga necessário para controle do sangramento foi semelhante entre cirróticos e não cirróticos, mas o declínio nos níveis de hemoglobina, o volume transfusional requerido e o tempo de

Instituição: Departamento de Pediatria da Faculdade de Ciências Médicas da Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brasil

¹Mestre em Saúde da Criança e do Adolescente pela Faculdade de Ciências Médicas da Unicamp; Professora Assistente da Disciplina de Pediatria da Universidade Federal de Sergipe (UFS), Aracaju, SE, Brasil

²Doutora em Saúde da Criança e do Adolescente pela Faculdade de Ciências Médicas da Unicamp; Professora Assistente do Departamento de Pediatria da Faculdade de Ciências Médicas da Unicamp, Campinas, SP, Brasil

Endereço para correspondência:

Daniela Gois Meneses

Avenida Paulo VI, 299, Parque Residencial Beira Rio – Inácio Barbosa
CEP 49040-460 – Aracaju/SE

E-mail: daniela.meneses@ig.com.br

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internação foram maiores nos pacientes com cirrose, embora sem diferença estatística. Essas mesmas variáveis não se modificaram em relação aos dois diferentes esquemas de infusão da droga: com dose de ataque ou iniciando com dose de manutenção. Insucesso terapêutico foi observado com maior frequência entre os pacientes cirróticos (33%). Hiperglicemia foi o único efeito colateral detectado durante a infusão.

Conclusões: A administração de octreotida em crianças e adolescentes com sangramento digestivo por hipertensão portal foi segura e efetiva no controle do sangramento agudo, independente da causa da hipertensão portal e do esquema de infusão.

Palavras-chave: octreotida; hemorragia digestiva; hipertensão portal; criança; adolescente.

RESUMEN

Objetivo: Describir la evolución clínica de los episodios de hemorragia digestiva en niños portadores de hipertensión portal, con y sin cirrosis, tratados con octreotida.

Métodos: Estudio retrospectivo y descriptivo de 26 episodios de sangramento digestivo en 17 pacientes (promedio de edad 8,6 años, variación de 7 meses a 18,9 años), en el periodo de 1998 a 2006, en un hospital terciario universitario. El diagnóstico de hipertensión portal fue establecido por ultrasonografía y la cirrosis fue confirmada por la histología y clasificada respecto a la gravedad por el score Child-Pugh.

Resultados: Las causas de la hipertensión portal fueron obstrucción extrahepática de la vena porta en 11/17 casos (64,7%) y cirrosis hepática en 6/17 (35,3%). El sangramento fue controlado en 14/17 pacientes (82,3%). El tiempo de infusión de la droga necesario para control del sangramento fue semejante entre cirróticos y no cirróticos, pero la caída en los niveles de hemoglobina, el volumen transfusional requerido y el tiempo de internación fueron superiores en los pacientes con cirrosis, aunque sin diferencia estadística. Esas mismas variables no se modificaron respecto a los dos distintos esquemas de infusión de la droga: con dosis de ataque o iniciando con dosis de mantenimiento. Fracaso terapéutico fue observado con mayor frecuencia entre los pacientes cirróticos (33,3%). Hiperglucemia fue el único efecto secundario detectado durante la infusión.

Conclusiones: La administración de octreotida en niños y adolescentes con sangramento digestivo por hipertensión portal fue segura y efectiva en el control del sangramento agudo, independiente de la causa de la hipertensión portal y del esquema de infusión.

Palabras clave: octreotide; hemorragia digestiva; hipertensión portal; niños; adolescentes.

Introduction

Extrahepatic portal vein obstruction due to thrombosis is the most common cause of non-cirrhotic portal hypertension and biliary atresia is the more prevalent cause of cirrhosis⁽¹⁾.

Gastrointestinal bleeding from esophageal varices is the main cause of morbidity in patients with portal hypertension, bleeding recurrence is very high and mortality varies from 30 to 50%⁽²⁾. During acute bleeding, in addition to measures of hemodynamic support, endoscopic treatment (sclerotherapy, band ligation, tissue adhesives such as cyanoacrylate) and specific drugs such as octreotide and somatostatin are used for controlling bleeding.

Octreotide is a synthetic somatostatin that has been shown to reduce splanchnic blood flow in healthy volunteers and hepatic venous pressure in cirrhotic patients^(3,4). Thus, it has been used for variceal bleeding. This drug has a marked clinical importance for patients awaiting endoscopy for esophageal varices diagnosis and treatment, for patients presenting voluminous bleedings that impair visibility during the endoscopy, and for patients under increased rebleeding risk and who require the drug hypotensive effect for some days⁽⁵⁾. Few studies have focused the use of octreotide in pediatric patients.

This study aimed to describe clinical data in children and adolescents with portal hypertension, with and without cirrhosis, who were treated with octreotide during acute gastrointestinal bleeding, and to evaluate eventual differences between the use or not of a bolus dose.

Method

Twenty patients were seen between March 1998 and December 2006 at the University Hospital in Faculty of Medical Sciences, Unicamp. Patients aged 7 months up to 18 years. All had portal hypertension diagnosis based on ultrasonographic criteria, presented upper gastrointestinal bleeding and received octreotide to control acute bleeding episodes. Three patients were excluded because their records were incomplete.

A retrospective and descriptive study was conducted. Patients were classified as cirrhotic or non-cirrhotic. The diagnosis of cirrhosis was based on histological data. Ultrasound was performed using a Toshiba Power Vision 6000 apparatus equipped with 3.75-MHz sectorial and 5-MHz

linear transducers. The following parameters were evaluated in order to diagnose portal hypertension: splenomegaly, gallbladder wall thickness, small omentum thickness close to the venous ligament, small omentum/aorta ratio, and presence of splenorenal shunt⁽⁶⁻⁹⁾.

The Child-Pugh score⁽¹⁰⁾ was used to determine the severity of liver disease in cirrhotic patients. The following parameters were evaluated: serum albumin and bilirubin levels, prothrombin time, presence of ascites and encephalopathy. According to the routine of the service, the presence of coagulopathy and thrombocytopenia was investigated by INR measurement and platelet count. Vitamin K, fresh frozen plasma and platelets were replaced as needed. Requirement of blood transfusion was recorded.

The origin of bleeding identified by endoscopy was registered. If in the source could not be identified, the site of bleeding was classified as indeterminate. Associated endoscopic treatment was also recorded. Endoscopy was performed with a Pentax or Olympus videoendoscope. Sclerotherapy or band ligation was indicated in patients with active bleeding of esophageal varices and/or bleeding of medium and large size esophageal varices even in the absence of active bleeding. Cyanoacrylate was administered in some cases of bleeding from gastric varices.

The variables related to octreotide treatment were evaluated: dose, duration and side effects. Patients received a continuous intravenous infusion of 1-2µg/kg/h after an intravenous bolus dose (1µg/kg). The bolus administration was not universal. The criteria for the indication and duration of treatment were individually determined. The hospital stay in order to control bleeding was also recorded.

Rebleeding and treatment failure were defined as a new episode of bleeding, accompanied by a drop in hemoglobin levels during treatment or up to 15 days after the end of the last octreotide infusion. Control of glycemia, blood pressure and symptoms were performed in order to detect possible adverse effects during octreotide infusion.

Descriptive statistical analysis was performed, including measures of position and dispersion for continuous variables and frequency tables for categorical variables. Fisher's exact test was used to compare proportions. Continuous or ordinal variables were compared by Mann-Whitney test. A level of significance of 5% was adopted. All analyses were performed using the SPSS for Windows program, version 7.5. This study was approved by the Ethical Committee of the University.

Results

Twenty-six episodes of upper gastrointestinal bleeding due to portal hypertension occurred in 17 patients between March 1998 and December 2006. Patients age ranged from 0.56 to 18.9 years (mean: 8.64 and median: 7.91 years). The characteristics of the 26 upper gastrointestinal bleeding episodes are showed in Table 1.

Among the 17 patients, 8 (47.1%) were males; 6 (35.3%) had portal hypertension associated with cirrhosis, and 11 (64.7%) presented obstruction of the extrahepatic portal vein with normal liver function (associated with congenital hepatic fibrosis in one patient and with hepatoportal sclerosis in another).

Among the 26 bleeding episodes, six occurred were observed in cirrhotic patients and 20 in non-cirrhotic patients. Propranolol was used on the occasion of bleeding as primary prophylaxis in 4/26 (15.4 %) episodes and as secondary prophylaxis in 7/26 (26.9%).

Patients undergone endoscopy in all bleeding episodes. Octreotide was already being used by the patients on the occasion of the exam in 13/26 (50%) episodes. Only 5/26 (19.2%) episodes were characterized as active bleeding at the time of endoscopy, with octreotide already being used in 2 episodes. The site of bleeding was identified in 16/26 (61.5%) episodes: esophageal varices in 9, gastric varices in 3 and hypertensive gastropathy in 4. Endoscopic treatment was performed during 15/26 (57.7%) episodes: sclerotherapy (n=6) and band ligation (n=6) for esophageal varices and

Table 1 - Clinical data from 26 upper gastrointestinal bleeding episodes in 17 children and adolescents followed in a university hospital

	n (%)
Previous history of gastrointestinal bleeding	15 (57.7)
Propranolol previous use	11 (42.3)
Primary prophylaxis	4/11
Secondary prophylaxis	7/11
Previous sclerotherapy	15(57.3)
Previous band ligation	0
Site of bleeding	
Esophageal varices	9 (34.6)
Gastric varices	3 (11.5)
Hypertensive gastropathy	4 (15.4)
Indeterminate	10 (38.4)
Coagulopathy	16 (61.5)
Thrombocytopenia	16 (61.5)

cyanoacrylate (n=2) for the gastric varices. Sclerotherapy and cyanoacrylate were concomitantly applied during one of the episodes (Table 1).

A bolus dose of octreotide (ranged from 0.5 to 2.63µg/kg; mean: 1.19; median: 1µg/kg, P25/P75: 0.88/1.59) was administered during 20 of the 26 episodes. In the other cases, only a maintenance dose was infused. Some patients' weight was similar to adults weight so they received the maximum dose established by our protocol, conversely, in some cases the dose was lower than 1mcg/kg. The maintenance dose ranged from 0.44 to 1.43µg/kg/h (mean: 0.89, median: 0.92µg/kg/h, P25/P75: 0.73/1.00). The mean duration of treatment was 3.1 days (median: 3 days, P25/P75: 2.0/4.0) and the median of hospitalization was 6 days (P25/P75: 4.7/9.0). All patients received a proton pump inhibitor or H2 inhibitor during bleeding. Vitamin K replacement therapy was indicated in 16/26 (61.5%) episodes.

Blood transfusion was performed in 17/26 (65.4%) bleeding episodes, with the median hemoglobin drop of 3.27mg/dl (ranging from 0.74 to 6.50mg/dl). The mean transfusion volume was 23.8mL/kg of packed red blood cells (median: 16.4mL/kg, P25/P75: 10.84/30.3).

Hyperglycemia was the only side effect observed during 5 (22.7%) of 22 episodes. In all cases, hyperglycemia was reversed by gradual reduction of the octreotide dose without the need for insulin. In this study, 4 episodes that octreotide was administered simultaneously with glucose solution were excluded. The maximum level of blood sugar achieved was 169mg/dL.

Only 3/17 (17.6%) patients presented rebleeding. As shown in Table 2, one patient was not submitted to endoscopic treatment (patient 1). In this patient, rebleeding occurred from the esophageal varix on day 4 of treatment and was controlled by band ligation. The other two patients had undergone band ligation. One patient with Child C cirrhosis (patient number 2) maintained bleeding throughout the treatment and died. The other patient (patient number 3) presented bleeding on day 8 after the end of infusion.

No significant differences in the occurrence and the determination of site of active bleeding were observed between patients who received octreotide and those who did not receive the medication before the endoscopy. In the patients who received octreotide the active bleeding was present in 2 and the site of bleeding was determined in 9. In patients that did not receive octreotide before endoscopy, the active bleeding was present in 3 and the site of bleeding was determined in 7.

Comparison of patients who received bolus and maintenance doses of octreotide and those who received only the maintenance dose showed no significant differences regarding mean transfusion volume, mean drop in hemoglobin levels, duration of octreotide treatment or hospital length of stay (Table 3).

When bleeding episodes were compared between cirrhotic and non-cirrhotic patients, a higher drop in hemoglobin levels, a higher transfusion volume and a longer duration of hospital stay were observed in cirrhotic patients, but this difference was not significant. The time of use of octreotide was similar in the two groups (Table 4).

Treatment failure was observed for 2/6 bleeding episodes in cirrhotic patients and for 1/20 episodes in non-cirrhotic ones (Fisher's exact test, $p=0.12$). Frequency of side effects (hyperglycemia) was lower in cirrhotic patients, but no significant difference was observed between groups ($p=0.38$) (Table 5).

Discussion

The frequency of gastrointestinal bleeding in children with portal hypertension is higher in those with extra-hepatic portal vein obstruction than in cirrhotic patients. Portal vein obstruction is responsible for about 70% of all pediatric patients with portal hypertension⁽¹¹⁾. In the present study, 64.7% of the patients had portal hypertension due to extra-hepatic portal vein obstruction and presented 20/26 (76.9%) episodes of gastrointestinal bleeding.

Table 2 - Site of bleeding, endoscopic treatment, etiology of portal hypertension, and period of rebleeding in three rebleeding patients

	Patient 1	Patient 2	Patient 3
Site of bleeding	Esophageal varices F3LsBcRs+	Esophageal varices F3LiBcRs+	Esophageal varices F2LsBcRs+
Endoscopic treatment	No	Band ligation	Band ligation
Period of rebleeding	Day 4 of treatment	Throughout treatment (2 days)	Day 8 post-treatment
Etiology	EHPVO	Hepatitis C	AIH

EHPVO: extrahepatic portal venous obstruction; AIH: autoimmune hepatitis; F2: medium caliber varices; F3: large caliber varices; Li: locus inferior of esophagus; Ls: locus superior of esophagus; Bc: blue color of varices; Rs+: red sign present.

Table 3 - Blood volume transfused, decline in hemoglobin levels, time of use of octreotide and duration of admission according to the administration or not of a bolus dose of the drug

Bolus dose		Hemoglobin Decline	Duration of admission (days)	Time of use (days)	Blood transfusion volume (mL/kg)
Yes	n	19	20	20	13
	Mean	3.4	7.1	3.2	20.7
	Median	3.4	6.0	3.0	15.0
	P25	2.6	5.0	3.0	9.9
	P75	4.5	9.0	4.0	30.3
No	n	5	6	6	4
	Mean	3.8	6.0	2.8	33.5
	Median	3.1	4.5	2.0	19.8
	P25	2.1	3.7	1.3	12.9
	P75	5.7	7.5	4.7	67.9
<i>p</i> *		0.8	0.1	0.3	0.4

*Mann-Whitney test.

Table 4 - Blood volume transfused, decline in hemoglobin levels, time of use of octreotide and duration of admission in cirrhotic and non-cirrhotic patients

Cirrhosis		Hemoglobin Decline	Length of stay in hospital (days)	Time of use (days)	Transfusion volume (mL/kg)
Yes	n	5	6	6	4
	Mean	4.2	8.3	3.2	31.5
	Median	4.5	7.5	2.5	29.8
	P25	2.5	4.7	2.0	17.2
	P75	5.7	11.5	5.0	47.4
No	n	19	20	20	13
	Mean	3.3	6.4	3.1	21.4
	Median	3.1	5.5	3.0	14.5
	P25	2.3	4.25	2.25	9.9
	P75	3.9	8.0	4.0	26.1
<i>p</i> *		0.33	0.3	0.97	0.13

*Mann-Whitney test.

Table 5 - Distribution of the clinical data of bleeding episodes according to the presence or absence of liver cirrhosis

	Cirrhotic	Non-cirrhotic	<i>p</i> *
Blood transfusion	4/6	13/20	1.0
Active bleeding at endoscopy	1/6	4/20	1.0
Treatment failure	2/6	1/20	0.123
Side effects	1/6	8/20	0.380

Active bleeding was observed during the endoscopic exam in only 5/26 (38%) bleeding episodes analyzed at this study. Despite the small number of patients, no statistical differences were observed between episodes previously treated with octreotide and those untreated. This finding supports the hypothesis that bleeding ceases spontaneously in many cases. D'Amico *et al*⁽¹²⁾ reported spontaneous cessation of bleeding in 40 to 50% of adult patients with upper gastrointestinal bleeding due to portal hypertension.

In children, Eroglu *et al*⁽¹³⁾ noted the absence of active bleeding during endoscopic examination in 71% of episodes that occurred in patients under treatment with octreotide, but the percentage of cases in which bleeding cessation was spontaneous or secondary to the use of the medication could not be determined.

Some studies show that bolus administration of octreotide to clinically stable cirrhotic patients causes systemic vasoconstriction, a transient decrease in the hepatic venous pressure gradient

and a significant reduction of cardiac output^(3,5). However, in the present study, the administration of a bolus dose did not modify significantly the mean transfusion volume, mean hemoglobin decline, duration of octreotide treatment or hospital stay.

The only side effect detected during the administration of octreotide was hyperglycemia. In a meta-analysis on octreotide for acute esophageal variceal bleeding, Corley *et al*⁽¹⁴⁾ observed a frequency of hyperglycemia ranging from 0 to 23%. In another meta-analysis, Bañares *et al*⁽¹⁵⁾ compared endoscopic treatment with endoscopic treatment combined with pharmacological therapy for the control of acute variceal bleeding and found that hyperglycemia was the only adverse effect in the studies analyzed, with this side effect being significantly more frequent in the group of patients that underwent pharmacological treatment. However, the use of somatostatin and its derivatives (e.g., octreotide) was considered to be safe in view of the finding that none of the patients required discontinuation of therapy⁽¹⁵⁾.

Regarding the three patients who presented rebleeding, two had cirrhosis classified as Child C and the other underwent endoscopic treatment until the occurrence of rebleeding. Probably, the episodes of rebleeding were mainly related to the severity of the underlying disease and to the need of a definitive treatment rather than a medication effect.

Comparison of the bleeding episodes between cirrhotic and non-cirrhotic patients showed that the drop in hemoglobin levels, the blood transfusion volume, and hospital stay were slightly greater and in cirrhotic patients, although no statistical significance was observed, probably due to the

small number of patients in groups. This finding is probably related to the clinical severity of patients with cirrhosis who, in addition to impaired hepatic function, often present malnutrition and impaired general health.

Comparison of the present results with other studies is limited by the characteristics of the series, i.e., a pediatric population in which the main cause of upper gastrointestinal bleeding due to portal hypertension was extra-hepatic portal vein obstruction. Most studies evaluating octreotide were conducted on adults with cirrhosis and patients with gastrointestinal bleeding not related to portal hypertension⁽¹⁶⁾. Similar results in terms of the decline in hemoglobin levels, transfusion volume and duration of treatment were reported in a study of pediatric patients⁽¹³⁾.

The present report has limitations regarding its retrospective design and a small number of patients, however, it differs from international series due to the lower frequency of rebleeding, treatment failure and mortality. The effect of cirrhosis and hepatic insufficiency on the occurrence of rebleeding should be investigated in multicenter studies of patients with different demographic characteristics. Larger cohort studies are necessary to determine the benefits of combined or single treatment with octreotide in children, irrespective of the etiology of portal hypertension.

The use of octreotide in children and adolescents with portal hypertension with or without cirrhosis was considered safe. The drug seems to be effective in controlling acute bleeding in patients with portal hypertension, irrespective of etiology and the infusion schedule.

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