Turk J Gastroenterol 2004; 15 (3): 137-143

Efficacy of five days of subcutaneous octreotide treatment after sclerotherapy in preventing rebleeding from esophageal varices

Skleroterapi sonrası beş gün boyunca subkutan oktreotide tedavisinin özofagus varis kanaması tekrarı üzerine etkisi

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Background/aims: *Acute variceal bleeding is the most severe consequence of portal hypertension. Mortality due to bleeding among cirrhotic patients is high; between 30 and 50% die within six weeks of the first bleeding episode. This dismal outcome has led to attempts both to stop acute bleeding and to prevent rebleeding. The aim of this study was to investigate the efficacy of subcutaneous octreotide treatment, administered after emergency sclerotherapy, in preventing rebleeding of esophageal varices* ***Methods:*** *After a bolus injection of 50 microgram octreotide, 34 patients, forming the standard therapy (ST) group, received octreotide infusion at a rate of 50 microgram/h until endoscopic sclerotherapy performed within 36 hours. The same procedure was applied to another 27patients in the maintenance therapy (MT) group in which octreotide was given at 100 microgram 18h via subcutaneous (sc) route after sclerotherapy for five days. In both groups, sclerotherapy was repeated on the 5th-7th day. Patients were followed for three weeks for rebleeding.* ***Results:*** *Nine patients rebled in the ST group but only one patient bled in the MT group (3.7% vs. 26.5% vs. 3.7%; p<0.05). Transfusion requirement and duration of hospitalization period were similar in both groups.* ***Conclusions:*** *This study suggests that maintenance subcutaneous octreotide therapy is effective in controlling rebleeding episodes.*

Keywords: Esophageal varices, rebleeding, octreotide

Amaç: Akut özofagus varis kanaması portal hipertansiyonun en ciddi komplikasyonudur. Siroz hastalarında kanamaya bağlı mortalite oldukça yüksektir. Olguların %30-50'si kanama sonrası 6 hafta içinde kaybedilir. Bu kötü seyir akut ve tekrarlayan kanamaları önlemek için bir çok yöntemin geliştirilmesini teşvik etmektedir. Bu çalışmanın amacı acil skleroterapi sonrası başlanan subkutan oktretid tedavisinin özofagus varis kanaması tekarını önlemedeki etkisini araştırmaktır. ***Yöntem:*** *Olguların 34'ü standart tedavi grubunu oluştururken, 27 olgu da idame tedavisi grubunu oluşturmuştur. Tüm hastalara 50 mg iv bolus olarak verilen oktreotidi takiben, kanamayı izleyen 12-36 saat boyunca (endoskopik skleroterapi yapılana kadar) 50 mg I saat hızında oktreotid infüzyonu yapıldı. İdame tedavisi grubuna skleroterapi sonrasında beş-yedi gün süreyle sekiz saatte bir 100 mg deri altı oktreotid verildi. Her iki gruba da ilk skleroterapiden sonraki beş-yedinci günlerde ikinci skleroterapiler yapıldı. Gruplardaki kanama süresi (gün), transfüzyon sayısı (ünite), tekrar kanama süresi (gün), hastanede kalış süresi (gün) ve üç hafta içindeki mortalite durumu kaydedildi.* ***Bulgular:*** *Standart tedavi grubunda 5 hastada, idame grubunda ise 1 hastada varis kanaması tekrarı gözlendi (3,7% vs. 26.5%; p<0.05). Transfüzyon gereksinimi ve hastanede kalış süresi her iki grupta benzerdi. Sonuç: Bu çalışma subkutan oktreotid idame tedavisinin varis kanaması tekrarını önlemede etkin bir ilaç olduğunu göstermiştir.*

Anahtar kelimeler: Özofagus varisleri, tekrar kanama, oktreotid

INTRODUCTION

Gastrointestinal bleeding is the most severe complication of portal hypertension, and esophageal and gastric varices are by far the most common sources of bleeding in these patients. After an initial variceal hemorrhage, the frequency of recurrent bleeding ranges from 30% to 40% within the subsequent six weeks. The risk is maximal in the first five days, and then declines slowly over the first six weeks (1, 2). The mortality due to bleeding among these patients is high: approximately 50% die wit-

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Manuscript received: 22.04.2004 **Accepted:** 20.07.2004

hin six weeks of the first bleeding episode despite early diagnosis and treatment, and only 30% of the patients are alive three years later (3, 4). Therefore, all patients who have had an episode of bleeding must receive effective forms of treatment to prevent rebleeding. Vasoactive drugs, the Sengstaken-Blakemore tube, endoscopic variceal ligation, esophageal sclerotherapy, transjugular intraperitoneal shunt (TIPS) and surgical shunt procedures are current therapeutic options used in the management of bleeding esophageal varices. Vasopressin, terlipressin, somatostatin and octreotide are the vasoactive drugs that have been shown to achieve some efficacy in the control of acute variceal hemorrhage (5). Octreotide is a synthetic cyclic octapeptide. Trials have shown that the short-term efficacy of octreotide appeared to be comparable to that of sclerotherapy, variceal ligation and balloon tamponade. It was also reported that octreotide, when combined with sclerotherapy or variceal banding, improves bleeding control. Patients receiving combined therapy required significantly fewer transfusions. Mortality rates were also lower in the combined therapy groups (6-16). However, there are studies in the literature suggesting that although initial homeostasis is good with octreotide, rebleeding increases progressively with time (17, 18).

This study was designed to reveal the effects of subcutaneous (sc) octreotide maintenance therapy in controlling acute esophageal variceal bleeding and in preventing early rebleeding.

MATERIALS AND METHODS

Selection of patients

From January 1997 to January 2000, patients admitted to Erciyes University School of Medicine, Department of Gastroenterology, because of esophageal variceal bleeding were assessed for inclusion in the trial. The diagnosis of cirrhosis was based on signs of unequivocal liver damage assessed by clinical, biochemical, histopathological and ultrasonographic data present on enrollment or on a previous admission. The eligibility criteria were (1) age between 18 and 70 years old; (2) clinical evidence of bleeding (hematemesis and/or melena) during the previous 24 hours; and (3) endoscopically proven hemorrhage from esophagogastric varices. The diagnosis of hemorrhage from varices was based on the endoscopic visualization of an actively bleeding varix (oozing or spurting), a fresh clot or eschar on the surface of the varix, fresh blood in the stomach or the presence of esophageal varices in the absence of any other possible bleeding site in the upper gastrointestinal tract.

Exclusion criteria were a history of severe cardiovascular disease, including acute myocardial infarction, atrioventricular block, heart failure, chronic peripheric ischemia, and arterial hypertension (defined by a systolic blood pressure over 170 mmHg and/or a diastolic blood pressure over 95 mmHg); a known hypersensitivity to drugs; chronic renal failure; and ongoing treatment for bronchial asthma.

The study protocol conformed to the Helsinki Declaration, and was approved by the Ethics Committee of Erciyes University Hospital. Informed consent was obtained from the patients or their relatives in some cases.

Clinical Assessment and General Management

Before the study, clinical history and findings on physical examination, electrocardiography, chest radiography, and complete laboratory analysis were recorded. Laboratory determinations included hematological parameters (hematocrit and hemoglobin values, red and white blood cell counts, platelet count and prothrombin activity), blood chemistry (concentrations of total protein, plasma albumin, plasma g-globulin, total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyltransferase, blood urea nitrogen, creatinine, uric acid, cholesterol, triglycerides, blood glucose, and sodium and potassium in plasma), and urinalysis (Table 1).

Patients were closely monitored during the whole period of the study. A nasogastric tube was placed for examination of the gastric content. Blood pressure and heart and respiratory rate were recorded hourly. Hematocrit was determined every six hours. Vital signs and urine outputs of patients were monitored closely. During resuscitation, patients with unstable vital signs and massive bleeding were transfused and fresh-frozen plasma or platelets, or both, were administered to patients with defects in coagulation. In addition, all patients received oral lactulose as prophylaxis of the hepatic encephalopathy and norfloxacin for intestinal decontamination.

Definitions

Complete control of bleeding was defined by stability of blood pressure, stability of hemoglobin

Table 1. Laboratory data of patients in both groups before treatment

	MT (n: 34) X±SD	ST (n: 27) X±SD		
Glucose (mg/dl)	108.03±37.83	113.70±40.89	0.56	>0.05
BUN (mg/dl)	21.20±5.74	23.33±7.03	1.30	>0.05
Cr (mg/dl)	0.82±0.31	0.90±0.31	0.97	>0.05
Na (mM/L)	137.35±4.07	137.44±4.33	0.08	>0.05
K (mM/L)	4.20±0.46	4.21±0.43	0.09	>0.05
Cl (mM/L)	102.38±7.00	102.22±4.38	0.10	>0.05
AST (IU/L)	50.47±29.14	59.55±38.61	1.05	>0.05
ALT (IU/L)	37.20±20.35	48.92±50.43	1.24	>0.05
T.Bil (mg/dl)	1.80±2.00	2.59±2.96	1.25	>0.05
PT (sec)	16±3.87	22.92±13.93	2.50	<0.05
Albumin (g/dl)	3.14±0.57	3.07±0.50	0.53	>0.05
Hemoglobin (g/dl)	8.73±1.44	8.39±1.30	0.95	>0.05
Platelet (/mm^3)	105852.90±50432.7	84722.22±43012.1	1.73	>0.05
Urine volume (ml/24h)	1327.94±488.07	1509.26±658.82	1.23	>0.05
Urine gravity	1021.32±5.55	1018.52±7.44	1.69	>0.05

concentration (measured twice daily), stability of hematocrit level (measured every 6 hours) and no further transfusion requirement.

Rebleeding was defined by (a) presence of bright red hematemesis in gastric or esophageal aspirate, and (b) active variceal hemorrhage seen on endoscopy.

Inadequate response to octreotide was defined as (a) hemodynamic instability, and (b) transfusion of five or more packed red blood cells for vital stabilization within 12 hours from beginning of i.v. octreotide infusion.

Treatment Protocol and Patients

Endoscopic examinations were performed during active hemorrhage or within 36 hours as a consequence of coma or shock. Balloon tamponade was performed if patient had massive hemorrhage or endoscopy was not feasible because of coma or shock. Olympus GIF type Q 10 endoscope (Olympus, Tokyo, Japan) was used for sclerotherapy. The sclerosing solution was 1% polydokanol (Aethoxysklerol®, Kreussler, Germany). Varices were injected circumferentially at the gastroesophageal junction with a total of 0.5 to 2 ml of sclerosing solution per varix, not exceeding a total of 20 ml per sclerotherapy session.

Seventy-five patients with acute esophageal variceal bleeding were included in the study and i.v. octreotide was given. In 14 (18.7%) patients, bleeding could not be controlled within 24 hours and these patients died (Table 2). As a result, bleeding control was achieved in 81.3% of patients within 24 h. After 50 microgram of intravenous bolus injection, octreotide was infused at a rate of 50 microgram/h to 34 patients forming the standard therapy (ST) group, until endoscopic sclerotherapy performed within 36 hours. The same procedure was applied to another 27 patients in the maintenance therapy (MT) group in which octreotide was given at 100 microgram/8h via sc route after sclerotherapy for five days. Therefore, 61 consecutive active variceal bleeding episodes were randomly assigned to either standard octreotide treatment group (ST) or octreotide maintenance group (MT). In both groups, sclerotherapy was repeated on the 5th-7th day.

Table 2. Clinical characteristics of patients in whom initial intravenous octreotide therapy failed

Patients, n		**14**	
Gender	Female	3	%21.4
	Male	11	%78.6
Etiology			
	Ethanol	2	%14.3
	Viral	10*	%71.4
	Cryptogenic	2	%14.3
Child- Pugh Classification			
	A	1	%7.1
	B	7	%50.0
	C	6	%42.9
Duration of cirrhosis (years)			
	< 1	2	%14.3
	1-5	8	%57.1
	> 5	4	%28.6
Bleeding episode			
	First	7	%50.0
	>2	7	%50.0

* HCV: 7 HBV: 3

Follow-up

A complete evaluation, including physical examination, electrocardiography, and laboratory determinations (hematological parameters, blood chemistry, and urinalysis), was performed 24 hours after stopping the trial (Table 3). The patients were observed for rebleeding throughout three weeks and results were recorded.

Table 3. Laboratory data of patients in both groups after treatment

	ST Group X±SD (n: 34)	MT Group X±SD (n: 27)		
Glucose (mg/dl)	114.59±38.01	120.33±43.84	0.55	>0.05
BUN (mg/dl)	24.70±16.69	34.85±20.10	2.11	<0.05
Cr (mg/dl)	0.96±0.68	1.12±0.53	1.01	>0.05
Na (mM/L)	136.62±4.44	138.67±6.06	1.52	>0.05
K (mM/L)	4.12±0.45	4.51±0.85	2.16	<0.05
Cl (mM/L)	101.91±5.47	102.70±5.23	0.57	>0.05
AST (IU/L)	80.73±166.69	60.70±31.51	0.61	>0.05
ALT (IU/L)	86.88±247.41	62.00±73.50	0.50	>0.05
T.Bil (mg/dl)	3.25±4.19	2.75±2.97	0.52	>0.05
PT (Sec)	16.94±3.66	23.70±15.17	2.26	<0.05
Albumin (g/dl)	3.14±0.46	3.08±0.60	0.45	>0.05
Platelet (/mm^3)	100323.5±51587.36	73370.3±38729.98	2.25	<0.05
Urine volume (ml/24h)	1350.3+383.6	1538.9±694.3	1.26	>0.05
Urine gravity	1019.4±4.0	1019.4±4.9	0.03	>0.05

RESULTS

There were no statistically significant differences between the ST and MT groups as to age, sex, severity or duration of liver disease, etiology and number of patients with first variceal bleeding or more than one variceal hemorrhage (Table 4). Cirrhotic patients had additional illnesses in both groups (Table 5). Esophageal varices were classified according to three grades (5). There was a statistically significant difference as to the size of esophageal varices between the two groups. The number of patients with grade II varices was greater in the ST group (p<0.05) (Table 6).

Bleeding control

Bleeding was controlled in 81.3% of patients on initial admittance. Bleeding period was 1.7±0.67 vs. 1.6±0.57 days in ST and MT groups, respectively (p>0.05).

Table 4. Clinical characteristics of patients

Factors	ST Group (n=34)	MT Group (n=27)	p value
Age (yr ± SD)	53.8±13.8	57.1±12.4	NS
Sex (M/F), n	23/11	16/11	NS
Etiologies of cirrhosis, n			NS
HBV	9	8	
HCV	10	8	
Cryptogenic	8	6	
HBV + HDV	2	1	
Ethanol	5	4	
Child-Pugh Classification, n			NS
A	16	10	
B	15	8	
C	3	6	
Duration of cirrhosis, years			NS
<1	15	8	
1-5	12	15	
>5	7	1	
Bleeding episode			NS
First one	18	11	
>2	16	13	

NS: p>0.05

Table 5. Additional diseases in ST and MT groups

	ST		MT	
	n	%	n	%
Diabetes Mellitus	5	14.7	6	22.2
Diabetes Mellitus+Hypertension	1	2.9	3	11.1
Peptic Ulcus	1	2.9	1	3.7
Hypertension	2	5.9	1	3.7
COPD	3	8.8	0	0
Hypertension + COPD	1	2.9	0	0
Diabetes Mellitus+COPD	1	2.9	0	0
Disease-free	20	58.8	16	59.3
TOTAL	34	100	27	100

COPD: chronic obstructive pulmonary disease

Table 6. Grade of varices in both groups

	ST Group (n: 34)	MT Group (n: 27)	X2	p
Grade I	3 (8.8%)	0		
Grade II	13 (38.2%)	3 (11.1%)	9.42	<0.05
Grade III	18 (52.9%)	24 (88.9%)		

Rebleeding

In the hospitalization period, fewer MT group patients experienced rebleeding from their varices compared with ST group patients. Nine patients rebled in the ST group but only one patient bled in the MT group at the 6th day; that patient died immediately after the maintenance sc octreotide therapy was stopped (26.5% vs. 3.7%; p<0.05). Rebleeding occurred within *1.1±2.11* days. If we regard the term early rebleeding as occurring within five days from the first episode, only one patient in the ST group had early rebleeding, which occurred on day five after the first sclerotherapy. On the other hand, 4, 1, 1 and 2 cases rebled on days 6, 7, 10 and 12, respectively. It is necessary to take into consideration that all rebleeding episodes were severe and could not be controlled and the patients died.

Transfusions

The mean packs of blood transfused to the patients of groups ST and MT were 4.23±2.90 packs and 3.03±2.07 packs, respectively ($p>0.05$). There was no statistically significant difference between the two groups. The amount of blood transfused in the patients who rebled was 5.8±3.61 packs and in those who did not rebleed, 3.45±2.18 packs ($p>0.05$).

Duration of hospitalization

The mean hospital stay of the ST group was 7.2±2.9 days, versus 7.1±1.9 days ($p>0.05$) in the MT group. There was no statistically significant difference between the two groups.

Mortality

Nine ST group patients vs. one MT group patient died among those who received either emergency sclerotherapy or insertion of a Sengstaken-Blakemore tube. Thus, mortality rate was higher in the ST compared to MT group (26.5% vs. 3.7%; $p<0.05$). Overall mortality rate was 32% (24/75 patients) in our study.

Complications

Serum glucose (113.7±40.9 VS.120.3± 43.8; $p< 0.01$), BUN (22.3±7 vs. 34.8±10.1; $p<0.05$), and creatinine (0.9±0.3 vs. 1.12±0.5; $p<0.05$) levels increased and number of platelets (84722.2±43102 vs. 73370.3±38729, 9; $p<0.05$) decreased compared to pretreatment levels in the MT group at the end of the therapy with sc octreotide. However, only serum glucose levels (108.0±37.8 vs. 114.6±38.0; $p<0.01$) increased in the ST group compared to initial biochemistry values.

Statistics

All results are expressed as mean±SD. Mann-Whitney U test, c2 test and Fischer's exact tests were used to compare the differences in values between the groups. All analyses were two-tailed and were conducted using computer-based statistical software (SPSS® for Windows® 9.0); p value less than or equal to 0.05 was accepted as statistically significant.

DISCUSSION

The main targets in the management of cirrhotic patients with variceal bleeding are to stop acute bleeding and then to prevent early rebleeding from varices, which occurs generally within 5-14 days after first bleeding (1-5). Emergency sclerotherapy, band ligation or TIPS cannot be performed in most hospitals. In these settings, pharmacotherapy has a vital role in hemodynamic stabilization and the prevention of deterioration in liver functions. A great many publications have set forth that vasoactive drugs, especially somatostatin, terlipressin or octreotide, might be used with confidence in the treatment of acute bleeding episodes caused by esophageal varices (6, 8-11, 13, 14, 19-21).

There are papers in the literature that compare the effect of octreotide in stopping acute esophageal variceal bleeding and preventing the rebleeding period with vasopressin, somatostatin, terlipressin, balloon tamponade, sclerotherapy and band ligation (13, 14, 17, 22-25).

Our study was designed to investigate the effect of maintenance sc octreotide treatment, which was given after octreotide infusion and first sclerotherapy session and stopped after second sclerotherapy session performed on the fifth or seventh day of acute variceal bleeding. This study was different in part from studies that have searched the outcomes of octreotide in the management of variceal bleedings since octreotide was given via subcutaneous route throughout five days instead of continuous infusion to prevent rebleeding. The results of the present study confirmed that octreotide is indeed highly effective for the treatment of acute variceal bleeding (81.3%), a finding that is in agreement with previous studies using this drug (13, 14, 17, 22-25).

Contrary to the literature, there was no statistically significant decrease in the requirement of blood transfusion or length of hospital stay in the MT group. This data may be explained by the study protocol since all cases were on i.v. octreotide infusion until sclerotherapy was performed; short duration of therapy with octreotide infusion may have had a positive effect on those parameters in the ST group. Management of variceal bleeding is considerably difficult. Prevention of rebleeding and mortality are the aims of clinicians in the hospitalization period of cirrhotic patients. However, there are conflicting results about the effectiveness of octreotide in the control of rebleeding. In some trials (17, 18), more patients in the octreotide-treated group rebled after 12 hours, while in other trials octreotide seemed to be effective in controlling rebleeding, particularly throughout five days (13, 14, 17, 22-25). The risky period for variceal rebleeding is accepted as the first six

weeks after acute bleeding (1, 2). In this study, only one case in the ST group rebled within five days; however, one patient in the MT group and nine patients in the ST group rebled within 14 days ($p<0.05$). Rebleeding rate was higher in the ST group (26.5% vs. 3.7%). Afterwards, none of the cases in either group rebled during follow-up. Besson's study is similar in part to the present investigation. Control of acute bleeding, prevention of rebleeding and number of transfusions were better in the combination group compared to the control group (28). Zuberi et al. did not perform a second sclerotherapy in addition to maintenance i.v. octreotide treatment after controlling the acute variceal bleeding. Together with the increased control of acute bleeding, an important reduction in the total number of rebleeding episodes and of transfused blood units was also found in the octreotide group (29). In another study, treatment of patients with 50 microgram/12h sc octreotide for six months was found to be effective in preventing rebleeding compared to the control group in which only sclerotherapy was performed (25). However, D'Amico et al. could not establish any significant effect of a 15-day course of sc octreotide on early rebleeding in an unselected population of consecutive cirrhotic patients surviving an upper digestive bleeding episode from a portal hypertensive source (30). As shown previously, octreotide treatment significantly decreases mortality rates in patients with variceal bleeding, especially in the duration of hospitalization. A similar result was found in this study: 26.5% of patients in the ST group vs. 3.7% of patients in the MT group ($p=0.033$) died due to uncontrolled re-bleeding.

It is evident that esophageal variceal bleeding episodes severely deteriorate the life quality of cirrhotic patients. Every bleeding episode impairs liver reserves. In conclusion, this study suggests that sc octreotide therapy is effective in controlling acute bleeding episodes and may safely reduce the risk of rebleeding episodes.

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