Serum Angiotensin I-Converting Enzyme Levels and the Therapeutic Effects of Octreotide in Esophageal Variceal Hemorrhage

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Abstract: *Introduction:* The aim of this study is to investigate the relationship between serum angiotensin I-converting enzyme (ACE) levels and therapeutic effects of octreotide in the treatment of esophageal variceal hemorrhage (EVH) as a result of liver cirrhosis. *Methods:* Serum ACE levels were measured by ultraviolet light colorimetric analysis in 80 cases of liver cirrhosis with EVH before and after the treatment of various doses of octreotide (25 and 50 μg/hr treatment in 40 cases, respectively), which were compared with 20 healthy controls. *Results:* Between the octreotide treatment groups, there were no significant differences in the Child-Pugh score, the endoscopic severity of esophageal varices and ACE levels before octreotide treatment. Pretreatment levels of serum ACE were markedly higher in patients with EVH compared with healthy controls ($P < 0.001$). Serum ACE levels were significantly higher before octreotide treatment than 72 hours after treatment in patients with EVH. Serum ACE after octreotide treatment declined more evidently in the 50 μg/hr than in the 25 μg/hr treatment group. The hemostatic rate within 6 hours after octreotide treatment was significantly higher in the 50 μg/hr than in the 25 μg/hr treatment group. The rebleeding rate within 72 hours after octreotide treatment was markedly lower in the 50 μg/hr than in the 25 μg/hr treatment group. *Conclusions:* Octreotide treatment in patients with EVH can result in decreased serum ACE levels, which correlated with the dose of octreotide. The decline in serum ACE levels may be involved in the mechanisms by which octreotide lowers portal vein pressure in EVH treatment.

Key Indexing Terms: Esophageal varices; Liver cirrhosis; Angiotensin I-converting enzyme (peptidyl-dipeptidase A); Octreotide. **[Am J Med Sci 2011;342(1):20–23.]**

Angiotensin I-converting enzyme (ACE) can catalyze the transformation of angiotensin I to angiotensin II. Research has shown that the ACE plays a role in the pathogenesis of portal hypertension in liver cirrhosis[1] by increasing the levels of angiotensin II, which constricts blood vessels, resulting in increased resistance to portal blood flow.[2] ACE inhibitors can quickly lower portal pressure.[3] Zhang et al[1] have found that serum ACE levels decreased significantly in patients with liver cirrhosis after a portacaval shunt. Thus, the authors suggested that the decrease of ACE levels was probably associated with the decreased portal pressure.

Octreotide, a somatostatin analog, is an important medication in the treatment of esophageal variceal bleeding by effectively reducing portal pressure. Octreotide administered intravenously in doses of 25 to 50 μg/hr has been found to have varying efficacy in the control of esophageal variceal hemorrhage (EVH).[4] Although the mechanisms by which octreotide lowers portal hypertension have been investigated before, the influence of octreotide on ACE or angiotensin II levels has not been well studied. In the current study, we focused on ACE levels because the levels of angiotensin II are significantly influenced by the effective systemic blood volume, which can change a great deal before and after treatment. In contrast, serum ACE levels do not depend on the blood volume, and therefore, provide more reliable measurements in patients with esophageal variceal bleeding before and after varying doses of octreotide.

METHODS

General Information

The protocol was approved by our institutional review board, and all patients signed written informed consents before starting the trial.

Eighty cases of liver cirrhosis with esophageal variceal bleeding were confirmed by endoscopy, including 48 men and 32 women aged 43 to 65 years, with an average age of 51.7 years. The patients, stratified by age and sex, were randomly divided into 25 and 50 μg/hr octreotide treatment groups. There was no primary heart, lung, kidney disease, hypertension or sarcoidosis in any of the cases.

Blood samples were collected[5] for the measurement of ACE levels before and 72 hours after treatment with octreotide in patients with esophageal variceal bleeding. On admission, routine blood tests of liver enzymes,[6] prothrombin time[7] and B-mode ultrasonography[8] were performed. The therapeutic protocol for octreotide administration was as follows: slow intravenous injection of 100 μg octreotide for 10 minutes, and then continuous intravenous drip by 25 or 50 μg/hr for 5 days. During the whole period of the study, no other drugs having the effects of reducing the pressure of the portal vein or ACE were used. The rate of hemostasis within 6 hours and the rate of rebleeding within 72 hours after the use of octreotide were determined. Balloon tamponade or endoscopic sclerotherapy of varices was performed if the bleeding could not be controlled by octreotide within 6 hours or if rebleeding occurred within 72 hours. The cases in which the bleeding could not be controlled by octreotide within 6 hours were removed from the rehemorrhage rate statistics. Blood samples from the control group were directly submitted to test ACE levels, which were determined by ultraviolet light colorimetric analysis. Detection kits were purchased from the Navy General Hospital, Beijing, China, and the assays were performed following the manufacturer's instructions.

Statistical Analysis

All measurement data were expressed as mean $\pm$ standard deviation. Paired and multiple grouped measurement data were analyzed by the Student t test and analysis of variance. Data were also analyzed by the χ^2 test.

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TABLE 1. Comparison of Clinical Parameters of Patients Who Received Octreotide Treatment for Esophageal Variceal Bleeding

Clinical Parameters	50 μg/hr Treatment Group	25 μg/hr Treatment Group	P
Gender			
Male (cases)	24	24	
Female (cases)	16	16	
Age	51.3 ± 4.7	52.1 ± 5.2	0.489
RBC count ($\times 10^{12}$/L)	2.52 ± 0.26	2.55 ± 0.22	0.618
Hb concentration (g/L)	71.6 ± 9.1	72.2 ± 9.3	0.762
Child-Pugh classification			
B (cases)	14	17	0.491
C (cases)	26	23	
Endoscopic severity of esophageal varices	All severe	All severe	
Portal vein diameter (mm)	12.9 ± 1.37	13.1 ± 1.38	0.572
ACE (U/L)	60.3 ± 7.7	58.4 ± 5.2	0.218

[a] Severity of varices is defined by the criteria of the Chinese Society of Digestive Endoscopy.

RBC, red blood cell; ACE, angiotensin-converting enzyme.

RESULTS

Each octreotide treatment group had 40 cases, with 24 men and 16 women. The 25 μg/hr treatment group ranged in age from 43 to 62 years, with an average age of 52.1 years. The 50 μg/hr treatment group ranged in age from 44 to 65 years, with an average age of 51.3 years. Twenty cases of controls were all healthy blood donors with 10 men and 10 women, aged 25 to 35 years, with an average age of 29 years.

Comparisons of clinical conditions between the treatment groups that received different doses of octreotide are shown in Table 1. No significant differences were found in age, sex, red blood cell count, hemoglobin, Child-Pugh classification, endoscopic grading of the severity of esophageal varices or portal vein diameter between the 2 treatment groups (all $P > 0.05$).

Comparisons of serum ACE levels between all the groups are shown in Table 2. There were no significant differences between the 25 and 50 μg/hr octreotide treatment groups of esophageal variceal bleeding ($t = 1.975$, $P > 0.05$). The serum ACE level of the control group was significantly lower than either of the 25 and 50 μg/hr octreotide treatment groups ($t = -30.750$, $P < 0.001$; $t = -30.725$, $P < 0.001$, respectively). In the 25 μg/hr octreotide treatment group, the serum ACE level 72 hours after treatment was significantly lower than that before treatment ($t = -18.300$, $P < 0.001$). In the 50 μg/hr octreotide treatment group, the serum ACE level 72 hours after treatment was significantly lower than that before treatment ($t = -28.725$, $P < 0.001$). The serum ACE level 72 hours after octreotide treatment was significantly decreased in the 50 μg/hr treatment group compared with the 25 μg/hr treatment group ($t = 9.825$, $P < 0.001$).

TABLE 2. Comparisons of Serum ACE Levels Between Various Treatment Groups

Group	ACE Levels Before Treatment (U/L)	ACE Level After Treatment (U/L)
50 μg/hr treatment	60.3 ± 7.7[a]	31.6 ± 6.5[b,c]
25 μg/hr treatment	58.4 ± 5.2[a]	40.1 ± 7.0[b]
Control	27.7 ± 7.8	

[a] vs. control group, $P < 0.001$.

[b] vs. ACE level before the treatment, $P < 0.001$.

[c] vs. ACE level of 25 μg/hr treatment group after the treatment, $P < 0.001$.

There were 31 Child B and 49 Child C class patients. Comparisons of serum ACE levels between groups of patients with varying liver function are shown in Figure 1. The mean serum ACE levels in both Child B (55.7 ± 5.3 U/L) and C (61.7 ± 6.3 U/L) patients before the treatment were significantly higher than those in the control group, respectively ($t = 28.027$, $P < 0.001$; $t = 34.087$, $P < 0.001$). As expected, the ACE level in Child C patients was significantly higher than that in Child B patients, with $t = 6.057$, $P < 0.001$.

Clinical criteria of hemostasis were normal blood pressure, heart rate stability, no hematemesis, and no recurrent melena maintained for at least 2 hours, warm and dry skin of limbs, urine production, normal red blood cell count and hemoglobin. The therapeutic results obtained from varying doses of octreotide are summarized in Table 3. Hemostasis within 6 hours after treatment was diagnosed in 34 of the 40 patients treated by 25 μg/hr octreotide (hemostatic rate, 85%), but rebleeding within 72 hours occurred in 7 patients (incidence of rebleeding, 20.6%). Hemostasis within 6 hours after treatment was diagnosed in 39 of 40 patients treated by 50 μg/hr octreotide (hemostatic rate, 97.5%), and rebleeding within 72 hours occurred in 2 of these 39 patients (incidence of rebleeding, 5.1%). Variceal hemorrhage was stopped after balloon tamponade, or endoscopic sclerotherapy was used in all patients in whom there was uncontrolled bleeding or rebleeding. The hemostasis rate within 6 hours after 50 μg/hr was significantly higher than that after 25 μg/hr octreotide treatment ($\chi^2 = 3.914$, $P < 0.05$). Moreover, the rebleeding rate within 72 hours after treatment was significantly lower in the 50 μg/hr than in the 25 μg/hr octreotide treatment group ($\chi^2 = 4.017$, $P < 0.05$).

DISCUSSION

The current study found that ACE levels were significantly increased in patients with liver cirrhosis, and positively related to the pressure of the portal vein, which suggested that ACE played a role in the pathogenesis of portal hypertension.[3] In this study, serum ACE levels were significantly higher in patients with esophageal variceal bleeding than in the healthy control group, which also supports the above view that ACE can also constrict the hepatic stellate cells and promote vascular smooth muscle hyperplasia to cause stenosis of the vascular lumen,[9] resulting in increased portal pressure. In addition, increased ACE can indirectly promote the production of aldosterone through angiotensin II, resulting in water and sodium retention, which may also increase portal pressure.[1]

In this study, serum ACE levels of patients with esophageal variceal bleeding apparently decreased after octreotide treatment, which suggests that octreotide application may result in the reduction of serum ACE. In liver cirrhosis, the mechanism of increased serum ACE levels is not clear. The possible mechanisms include increased release of ACE as a result of stimulation by hypoxemia[10] and reduced clearance of ACE because of impaired liver function.[11] Octreotide application in patients with liver cirrhosis may reduce portal pressure by the above mechanisms, thereby reducing visceral congestion,