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Acute Hemodynamic Effects of Octreotide and Terlipressin in Patients with Cirrhosis: A Randomized Comparison

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BACKGROUND: Octreotide and terlipressin are widely used in acute variceal hemorrhage to reduce the bleeding rate. They purportedly act by mesenteric arterial vasoconstriction, thus reducing portal venous flow (PVF) and portal pressure. Little is known about the immediate-early hemodynamic effects of these drugs.

AIM: To compare the acute hemodynamic effects of octreotide and terlipressin in patients with cirrhosis.

PATIENTS: Forty-two cirrhotic patients with a history of variceal bleeding were randomized to receive either octreotide 100 μg intravenous bolus followed by a continuous infusion at 250 μg/h (n = 21), or terlipressin 2 mg intravenous bolus (n = 21).

METHODS: Mean arterial pressure (MAP), heart rate (HR), hepatic venous pressure gradient (HVPG), and PVF, assessed by duplex Doppler ultrasonography, were measured before and at 1, 5, 10, 15, 20, and 25 min after the start of drug administration.

RESULTS: Octreotide markedly decreased HVPG ($-44.5 \pm 17.8\%$) and PVF ($-30.6 \pm 13.6\%$) compared to the baseline at 1 min ($p < 0.05$). Thereafter, both variables rapidly returned toward the baseline, and by 5 min, no significant differences in HVPG ($-7.1 \pm 28.9\%$) and PVF ($10.2 \pm 26.2\%$) were noted. A similar transient effect on MAP and HR was observed. Terlipressin significantly decreased HVPG ($-18.3 \pm 11.9\%$) and PVF ($-32.6 \pm 10.5\%$) at 1 min ($p < 0.05$) and sustained these effects at all time points. The effects on arterial pressure and HR were also sustained.

CONCLUSIONS: Octreotide only transiently reduced portal pressure and flow, whereas the effects of terlipressin were sustained. These results suggest that terlipressin may have more sustained hemodynamic effects in patients with bleeding varices.

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INTRODUCTION

Octreotide and terlipressin are probably the two most commonly used drugs worldwide to reduce the rate of acute bleeding from gastroesophageal varices in patients with portal hypertension (1–5). It is believed that both drugs act as mesenteric vasoconstrictors, thus reducing portal venous flow (PVF) and pressure (2, 6, 7). Octreotide is a synthetic octapeptide with pharmacologic actions similar to that of somatostatin. However, the therapeutic effect of octreotide on the portal and systemic hemodynamics in patients with liver cirrhosis is controversial. Some studies report favorable effects on portal hemodynamics with octreotide infusion, whereas others have failed to show any beneficial effects (8–12). Terlipressin or triglycyl lysine vasopressin is a synthetic long-acting analogue of vasopressin. It has been shown to induce systemic and mesenteric vasoconstriction, at least when examined between 30–240 min after administration (13–17).

To produce effective tamponade of actively bleeding varices, the ideal drug therapy should quickly reduce PVF and pressure, preferably within seconds to minutes. In view of this, it is somewhat surprising that virtually all previous hemodynamic studies of both drugs have examined their effects at 30–240 min after the start of administration. To date, there have been almost no studies focused on the immediate-early effects between 1–30 min. Therefore, the aim of the present study was to compare the immediate-early hemodynamic effects of standard doses of both octreotide and terlipressin on PVF and pressure in cirrhotic patients with a history of variceal bleeding.

Table 1. Clinical Characteristics of the Subjects

	Octreotide (n = 21)	Terlipressin (n = 21)	*p*
Age (years)	47.8 ± 7.4	49.5 ± 10.9	NS
Sex (male/female)	20/1	19/2	NS
Child-Pugh class (A/B/C)	9/11/1	9/8/4	NS
Child-Pugh score	6.9 ± 1.3	7.6 ± 1.9	NS
Etiology (alcohol/viral/combined)	15/2/4	15/3/3	NS
HVPG at baseline (mmHg)	16.1 ± 5.2	17.6 ± 4.1	NS
PVF at baseline (ml/mm)	683 ± 456	761 ± 409	NS
MAP at baseline (mmHg)	88.8 ± 13.9	86.3 ± 14.4	NS
HR at baseline (beats/min)	70.0 ± 9.8	69.2 ± 12.7	NS

HVPG, hepatic venous pressure gradient; PVF, portal venous flow; MAP, mean arterial pressure; HR, heart rate; NS, not significant.

PATIENTS AND METHODS

Study Cohort

The study included 42 cirrhotic patients with portal hypertension who had been hospitalized for acute variceal bleeding from December 2002 to January 2004. All the bleeding episodes in patients were managed by endoscopic variceal ligation and patients did not receive octreotide or terlipressin during the acute bleeding episode. The etiology of cirrhosis was alcohol-induced in 30 patients, chronic viral hepatitis in 5 patients, and both alcohol and viral hepatitis in 7 patients. The mean age of patients was 48.7 ± 9.3 yr, comprising 39 males and 3 females (Table 1). Patients with severe liver failure (serum bilirubin level >85 μmol/L), hepatic encephalopathy, severe arterial hypotension (mean arterial pressure (MAP) < 60 mmHg), hepatorenal syndrome, and ultrasonographic data suggesting a hepatocellular carcinoma and portal vein thrombosis were excluded from the study. No patients were taking drugs affecting hemodynamics such as β-blocker. The study was conducted according to the principles of the Declaration of Helsinki. The Ethics Committee of the Wonju College of Medicine university hospital approved the protocol, and the patients gave written informed consent.

Sample size calculations were performed presuming a mean reduction in hepatic venous pressure gradient (HVPG) from 5% to 50% from baseline and a 20% SD of HVPG reduction in both groups. To obtain a probability of obtaining an α-error = 0.05 and β-error = 0.10, 21 patients in each arm were required. The randomization was performed as follows: In total, 42 sets of the study medication were prepared: 21 sets containing octreotide (Sandostatin®, Novartis Pharma AG, Basle, Switzerland) and 21 sets containing terlipressin (Glypressin®, Ferring GmbH, Kiel, Germany). These sets were randomly numbered from 1 to 42 and prepared with the same in appearance. Patients were numbered chronologically from 1 to 42, according to the date of the randomization, and the corresponding set of the study medication was assigned.

Hemodynamic Measurements

Hemodynamic studies were performed 7 to 10 days after admission, when the gastrointestinal bleeding had ceased and the hemodynamic conditions had stabilized. The right hepatic vein was catheterized percutaneously through the femoral vein, and the pressure in both the wedged and the free position was recorded using a 7 Fr. balloon-tipped catheter (Arrow Deutschland GmbH, Postfach Erding, Germany). The portal pressure was estimated from the HVPG, which was determined by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure (8, 18, 19). The PVF was evaluated by Doppler ultrasonography (3.5 MHz convex probe, Aloka, Tokyo, Japan). Portal venous velocity and the cross-sectional area of the portal vein were estimated from a subcostal scan at its crossing point with the hepatic artery. When the sample point was adjusted to the center of the portal vein, the portal venous velocity was recorded during a quiet suspended expiration and was averaged over a few seconds. The PVF was determined by the formula: cross-sectional area × mean velocity × 60 (20). The coefficient of variation for the PVF measurements with this method in our center is 3% (21). The MAP was measured noninvasively with an automated sphygmomanometer (Hewlett-Packard M 1205A; Palo Alto, CA). The heart rate (HR) was derived from continuous electrocardiogram monitoring. The HVPG, PVF, MAP, and HR were measured before and at 1, 5, 10, 15, 20, and 25 min after a 100 μg octreotide intravenous bolus, followed by continuous infusion of 250 μg/h (n = 21), or a 2 mg terlipressin intravenous bolus (n = 21). No information for administrated drugs was provided to investigators by the end of study.

Statistical Analysis

All data are expressed as means ± SD. A repeated-measures analysis of variance (ANOVA) was used to investigate the changes in the HVPG and PVF after octreotide or terlipressin administration. Unpaired Student's *t*-test and χ^2 tests were used for statistical analyses of the differences between the octreotide and terlipressin group. A p-value < 0.05 was considered significant. All statistics were analyzed using the SPSS version 11.0 software (SPSS Inc., Chicago, IL).

RESULTS

There were no significant baseline differences between the octreotide and terlipressin groups in any variable (Table 1).

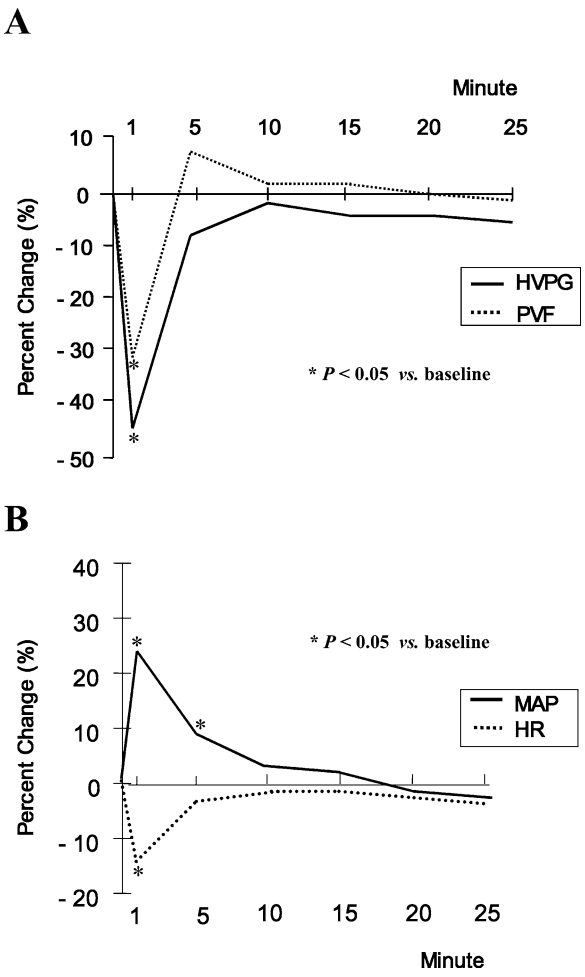

Figure 1. Effects of octreotide (100 μg bolus followed by continuous infusion of 250 μg/hr) on (*A*) hepatic venous pressure gradient (HVPG), portal venous flow (PVF) and (*B*) mean arterial pressure (MAP), heart rate (HR). Data are shown as percentage change from baseline. Octreotide significantly decreased HVPG and PVF at 1 min of its administration. However, HVPG and PVF rapidly returned toward the baseline, and at 5 min, no significant difference *versus* the baseline were noted. Changes in MAP were significant at 1 and 5 min, and significant change in HR was at 1 min.

Hemodynamic Responses with Octreotide

The 100 μg octreotide bolus, followed by continuous infusion of 250 μ/h significantly decreased both HVPG (from 16.1 $\pm$ 5.2 mmHg to 9.1 $\pm$ 4.5 mmHg, $-44.5 \pm 17.8\%$, $p < 0.05$ *vs* baseline), and PVF (from 683 $\pm$ 456 ml/min to 446 $\pm$ 264 ml/min, $-30.6 \pm 13.6\%$, $p < 0.05$ *vs* baseline) at 1 min (Fig. 1A). However, HVPG and PVF rapidly returned toward the baseline, and at 5 min, no significant difference *versus* the baseline were noted ($-7.1 \pm 28.9\%$, 10.2 ± 26.2, respectively, $p > 0.05$). A significant increase in MAP (from 88.8 $\pm$ 13.9 mmHg to 109.2 $\pm$ 22.1 mmHg, $23.8 \pm 14.2\%$, $p < 0.05$) and a decrease in HR (from 70.0 $\pm$ 9.8 beats/min to 59.8 $\pm$ 10.8 beats/min, $-14.6 \pm 10.1\%$, $p < 0.05$) occurred at 1 min. Thereafter, similar to the portal hemodynamic pattern, these changes in MAP and HR rapidly disappeared (Fig. 1B).

Hemodynamic Responses with Terlipressin

Terlipressin 2 mg bolus induced a significant decrease both in HVPG and PVF ($-18.3 \pm 11.9\%$, $-32.6 \pm 10.5\%$, respectively, $p < 0.05$ *vs* baseline) at 1 min, and these changes were sustained at all time points measured (Fig. 2A). MAP increased at 1 min after the terlipressin administration (from 86.3 $\pm$ 14.4 mmHg to 101.2 $\pm$ 16.5 mmHg, $17.5 \pm 8.5\%$, $p < 0.05$), whereas HR decreased (from 69.2 $\pm$ 12.7 beats/min to 59.6 $\pm$ 10.6 beats/min, $-13.3 \pm 9.1\%$, $p < 0.05$), and these changes also were sustained (Fig. 2B).

To compare the portal-hypotensive effects of octreotide and terlipressin in another manner, we calculated the area under the curve for the HVPG effects. The areas were 174.5 for octreotide and 837.9 for terlipressin. Consequently, the ratio of octreotide to terlipressin was 1:4.8 in area under the curve, confirming the greater magnitude of terlipressin effect on portal pressure.

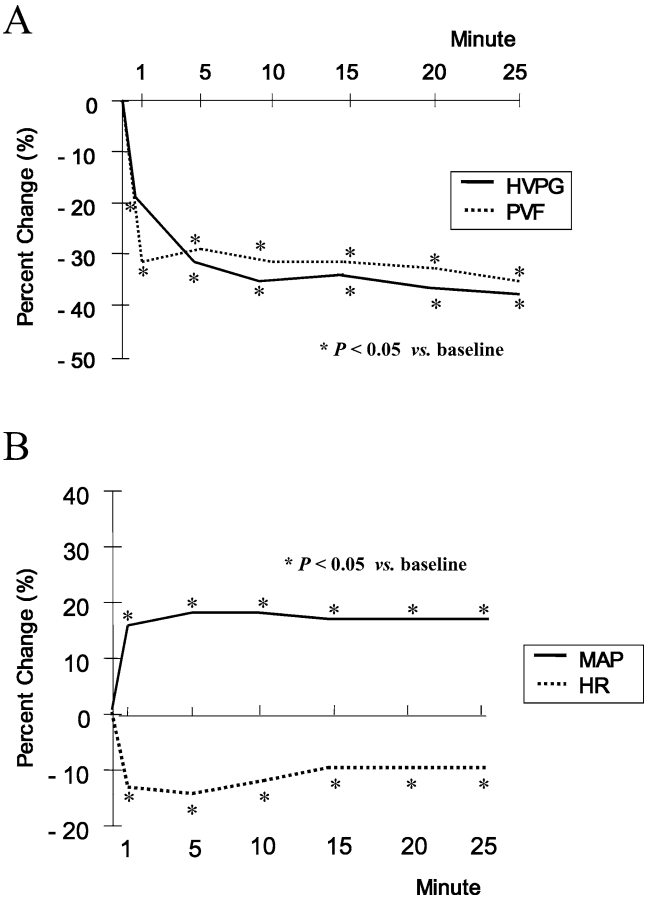

Figure 2. Effects of bolus injection of 2 mg terlipressin on (*A*) hepatic venous pressure gradient (HVPG), portal venous flow (PVF) and (*B*) mean arterial pressure (MAP), heart rate (HR). Data are shown as percentage change from baseline. Terlipressin significantly decreased HVPG, PVF, MAP, and HR at 1 min and these changes were sustained at all time points ($p < 0.05$).

DISCUSSION

Octreotide and terlipressin are both synthetic longer-acting analogues of the vasoconstrictor hormones somtatostatin and vasopressin, respectively. Moreover, both drugs reportedly decrease portal flow and pressure and are therefore used commonly to medically tamponade bleeding gastroesophageal varices. However, beyond these similarities, it is now clear that these drugs behave very differently in many respects. The literature on their efficacy in bleeding varices remains somewhat controversial, but recent reviews have suggested that some of the discrepancies result from inappropriately lumping together octreotide and somatostatin, and terlipressin and vasopressin, for metaanalytic reviews. More recent reviews including a Cochrane systematic review have avoided this mistake, correctly considering each individual drug by itself (3, 22). When analyzed in this manner, octreotide efficacy in acute variceal bleeding still remains unclear, whereas terlipressin is clearly an effective hemostatic agent (22). Moreover, in the Cochrane systematic review by Ioannou and colleagues, terlipressin was identified as the only drug that significantly improved mortality (3).

Even the acute hemodynamic studies of octreotide show discrepant results. Some studies report a beneficial effect on portal hemodynamics whereas others do not (8–12). In part, this may relate to the variable timing of the hemodynamic measurements after drug administration. In that regard, the immediate-early hemodynamic effects of octreotide are almost unstudied, with one notable exception (8). That exception is the study by Escorsell and colleagues (8), and the current results show a very similar transient pattern of octreotide effect on portal pressure and systemic hemodynamics. Additionally, we found that the transient portal pressure drop is directly proportionately related to a decrease in PVF, suggesting that the portal-hypotensive effect is entirely due to mesenteric vasoconstriction, rather than changing upstream intrahepatic resistance sites.

The exact mechanism of the rapid desensitization of the hemodynamic effect remains unclear. Octreotide has been postulated to act by inhibiting secretion of glucagons and other gastrointestinal vasodilatory peptides (23, 24). However, the very brief hemodynamic effect of the bolus octreotide contrasts with the prolonged suppression of glucagon secretion, which persists for many hours (8). This suggests that octreotide induces a direct systemic and splanchnic vasoconstriction. Indeed, recent studies have shown that octreotide directly vasoconstricts forearm vessels in cirrhotic patients, independent of the systemic hormonal effect of glucagons (25).

Previous studies have shown that octreotide also exerts a systemic effect with increased MAP and vascular resistance (8, 24, 26–29). This systemic effect was also observed in the present study, albeit again only in the immediate-early period, with rapid desensitization. Whatever the exact mechanism, this rapid desensitization raises doubt about the usefulness of octreotide and may explain the variability in previous studies about its efficacy in the management of acute variceal bleeding.

In contrast to octreotide, the hemodynamic effects of terlipressin in our study were sustained. We know from previous studies that after a single intravenous bolus of terlipressin, the hemodynamic effects persist between 30–240 min (13–17). Again, the immediate-early period including 1 min postdose has not been extensively studied. Romero and colleagues reported some measurements from the 3–60 min interval after terlipressin bolus administration in 13 patients (30). We previously reported the portal hypotensive effect of terlipressin in 43 patients from the 5–30 min interval postdose (18).

What is the clinical relevance of these short-term hemodynamic data? Besides the reduction in portal inflow and pressure, the other possible mechanisms of octreotide in the control of acute variceal bleeding include reducing postprandial splanchnic hyperemia and azygos vein flow, which were not assessed in the present study. Therefore, we cannot draw a definitive conclusion about whether octreotide is effective or not in variceal bleeding. However, we believe that the sustained effects of terlipressin on portal flow and pressure compared to the very transient effects of octreotide, provides a hemodynamic rationale to favor the former drug in the management of acute variceal bleeding.

Although a previous metaanalysis has concluded that octreotide treatment is ineffective in variceal bleeding (31), a recently published metaanalysis comparing octreotide with all other therapies came to the opposite conclusion, indicating that octreotide is superior to other treatments (2). However, there is a serious problem in many previous papers that demonstrate the efficacy of octreotide in variceal bleeding: lack of an untreated control group. All previous trials compared octreotide with other treatments such as vasopressin and endoscopic sclerotherapy or band ligation (4, 5, 32, 33). Episodes of variceal bleeding often cease without intervention; indeed the rate of spontaneous cessation of variceal bleeding can be as high as 50% (31). For this reason, a randomized clinical trial with an untreated control group is the only scientifically correct way to assess whether octreotide is effective. For ethical reasons, such a trial cannot be conducted.

Because our hemodynamic measurements were conducted 7–10 days after admission, when the bleeding had ceased and hemodynamics were stable, extrapolation of these results to the immediate and unstable bleeding situation should be done cautiously. Obviously, for ethical and logistical reasons, our study could not be performed in such hemodynamically unstable actively bleeding patients.

In summary, this prospective randomized hemodynamic study found that the effect of octreotide in reducing portal pressure and blood flow was transient compared to that of terlipressin in patients with cirrhosis.

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REFERENCES

1. D'Amico G, Pietrosi G, Tarantino I, et al. Emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis: A Cochrane meta-analysis. Gastroenterology 2003;124:1277–91.
2. Corley DA, Cello JP, Adkisson W, et al. Octreotide for acute esophageal variceal bleeding: A meta-analysis. Gastroenterology 2001;120:946–54.
3. Ioannou GN, Doust J, Rockey DC. Systematic review: Terlipressin in acute oesophageal variceal haemorrhage. Aliment Pharmacol Ther 2003;17:53–64.
4. Silvain C, Carpentier S, Sautereau D, et al. Terlipressin plus transdermal nitroglycerin vs. octreotide in the control of acute bleeding from esophageal varices: A multicenter randomized trial. Hepatology 1993;18:61–5.
5. Besson I, Ingrand P, Person B, et al. Sclerotherapy with or without octreotide for acute variceal bleeding. N Engl J Med 1995;333:555–60.
6. McCormick PA, Biagini MR, Dick R, et al. Octreotide inhibits the meal-induced increases in the portal venous pressure of cirrhotic patients with portal hypertension: A double-blind, placebo-controlled study. Hepatology 1992;16:1180–6.
7. Burroughs AK. Pharmacological treatment of acute variceal bleeding. Digestion 1998;59(Suppl 2):28–36.
8. Escorsell À, Bandi JC, Andreu V, et al. Desensitization to the effects of intravenous octreotide in cirrhotic patients with portal hypertension. Gastroenterology 2001;120:161–9.
9. Lin HC, Tsai YT, Lee FT, et al. Hemodynamic evaluation of octreotide in patients with hepatitis B-related cirrhosis. Gastroenterology 1992;103:229–34.
10. Moller S, Brinch K, Henriksen JH, et al. Effect of octreotide on systemic, central and splanchnic hemodynamics in cirrhosis. J Hepatol 1997;26:1026–33.
11. Eriksson LS, Brundin T, Söderlund C, et al. Hemodynamic effects of a long-acting somatostatin analogue in patients with liver cirrhosis. Scand J Gastroenterol 1987;22:919–25.
12. Pringle SD, McKee RF, Garden OJ, et al. The effect of a long-acting somatostatin analogue on portal and systemic haemodynamics in cirrhosis. Aliment Pharmacol Ther 1988;2:451–9.
13. Escorsell À, Bandi JC, Moitinho E, et al. Time profile of the haemodynamic effects of terlipressin in portal hypertension. J Hepatol 1997;26:621–7.
14. Lin HC, Yang YY, Hou MC, et al. Hemodynamic effects of a combination of octreotide and terlipressin in patients with viral hepatitis related cirrhosis. Scand J Gastroenterol 2002;37:482–7.
15. Therapondos G, Stanley AJ, Hayes PC. Systemic, portal and renal effects of terlipressin in patients with cirrhotic ascites: Pilot study. J Gastroenterol Hepatol 2004;19:73–7.
16. Vachiery F, Moreau R, Gadano A, et al. Hemodynamic and metabolic effects of terlipressin in patients with cirrhosis receiving a nonselective beta-blocker. Dig Dis Sci 1996;41:1722–6.
17. Valla D, Lee SS, Moreau R, et al. Effects of glypressin on the splanchnic and systemic circulation in patients with cirrhosis. Gastroenterol Clin Biol 1985;9:877–80.
18. Choi YJ, Baik SK, Park DH, et al. Comparison of Doppler ultrasonography and the hepatic venous pressure gradient in assessing portal hypertension in liver cirrhosis. J Gastroenterol Hepatol 2003;18:424–9.
19. Baik SK, Park DH, Kim MY, et al. Captopril reduces portal pressure effectively in portal hypertensive patients with low portal venous velocity. J Gastroenterol 2003;38:1150–4.
20. Schepke M, Raab P, Hoppe A, et al. Propranolol stereoisomer plasma concentrations and portal haemodynamic response in patients with liver cirrhosis. Aliment Pharmacol Ther 1999;13:1451–8.
21. Schiedermaier P, Hansen S, Asdonk D, et al. Effects of ursodeoxycholic acid on splanchnic and systemic hemodynamics: A double-blind, cross-over, placebo-controlled study in healthy volunteers. Digestion 2000;61:107–12.
22. Ferguson JW, Tripathi D, Hayes PC. Review article: The management of acute variceal bleeding. Aliment Pharmacol Ther 2003;18:253–62.
23. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: Variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Gastroenterology 2001;120:726–48.
24. Abraldes JG, Bosch J. Somatostatin and analogues in portal hypertension. Hepatology 2002;35:1305–12.
25. Chatila R, Ferayorni L, Gupta T, et al. Local arterial vasoconstriction induced by octreotide in patients with cirrhosis. Hepatology 2000;31:572–6.
26. Cirera I, Feu F, Luca A, et al. Effects of bolus injections and continuous infusions of somatostatin and placebo in patients with cirrhosis: A double-blind hemodynamic investigation. Hepatology 1995;22:106–11.
27. McCormick PA, Chin J, Greenslade L, et al. Cardiovascular effects of octreotide in patients with hepatic cirrhosis. Hepatology 1995;21:1255–60.
28. Gaudin C, Moreau R, Champigneulle B, et al. Short-term cardiovascular effects of somatostatin in patients with cirrhosis. Liver 1995;15:236–41.
29. Cerini R, Lee SS, Hadengue A, et al. Circulatory effects of somatostatin analogue in two conscious rat model of portal hypertension. Gastroenterology 1988;94:703–8.
30. Romero G, Kravetz D, Argonz J, et al. Terlipressin is more effective in decreasing variceal pressure than portal pressure in cirrhotic patients. J Hepatol 2000;32:419–25.
31. D'amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: An evidence-based approach. Semin Liver Dis 1999;19:475–505.
32. Hwang SJ, Lin HC, Change FG, et al. A randomized controlled trial comparing octreotide and vasopressin in the control of acute esophageal variceal hemorrhage. J Hepatol 1992;16:320–5.
33. Sung JJY, Chung SCS, Yung MY, et al. Prospective randomized study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. Lancet 1995;346:1666–9.