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Octreotide versus terlypressin in acute variceal hemorrhage in liver cirrhosis

Emergency control and prevention of early rebleeding

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Abstract. Sixty patients with endoscopically confirmed active variceal bleeding entered a randomized controlled clinical trial aimed at comparing the efficacy of octreotide vs. terlypressin in the control of acute variceal hemorrhage (period I, 24 h) and in the prevention of early rebleeding (period II, 6 days). Of the sixty 30 received octreotide (period I, 100 μg bolus followed by continuous intravenous infusion at 25 μg/h; period II, 100 μg t.i.d. subcutaneously), and 30 received terlypressin (period I, 2 mg intravenous bolus every 4 h; period II, 2nd day, 2 mg every 6 h; from 3th to 7th days, 1 mg every 6 h). Control of bleeding was achieved in 23 (76.6%) patients receiving octreotide and in 16 (53%) treated with terlypressin (NS); none of these patients suffered rebleeding during treatment. No significant difference in mortality was observed between the two groups during the hospitalization period. Complications due to therapy were lower with octreotide than with terlypressin ($P < 0.01$). Under the same effectiveness conditions the cost/benefit ratio must be taken into account.

Key words: Liver cirrhosis – Variceal bleeding – Octreotide – Terlypressin

Among the drugs proposed for the treatment of upper gastrointestinal bleeding in cirrhotics, alone or in association with conventional therapy (Sengstaken or Linton balloon, sclerotherapy), vasopressin and natural somatostatin has widely been used over the past 20 years with successful control of the bleeding [6, 18, 24]. Their beneficial effects are due to vasoconstriction of the splanchnic area which reduces blood flow and pressure in the portal venous system. High doses of somatostatin have been demonstrated to be more effective than placebo and at least as effective as vasopressin in controlling hemorrhages [4]. Nevertheless, the use of vasopressin is limited by the effect on heart and coronary arteries [2], while somatostatin must be administered at high doses and by continuous parenteral infusion because of its short half-life. In the search of new agents without these side effects a vasopressin analogue, triglycyllysine vasopressin (terlypressin), and a long-acting somatostatin analogue (octreotide) have recently been proposed.

This prospective randomized clinical trial was designed to compare these two vasoactive drugs during the acute bleeding and the hospitalization period following the acute hemorragic episode in cirrhotics with portal hypertension.

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Patients and methods

Patient selection

Between June 1990 and January 1993, 72 patients presenting with upper gastrointestinal bleeding were admitted to the Intensive Care Liver Unit of the Infectious Diseases Department of the University of Parma. Twelve of these were excluded because they did not fit the inclusion criteria (see below). A total of 60 consecutive patients were thus evaluated.

All patients had liver cirrhosis, previously diagnosed by laparoscopy and/or liver biopsy. A diagnostic esophagogastroduodenoscopy performed by experienced endoscopists within 6 h after admission revealed either active bleeding from esophageal or gastric varices or a single varix with stigmata of recent hemorrhage. Active variceal bleeding was defined by: (a) bleeding from esophageal or gastric varices visible at the time of endoscopy; (b) presence of a blood clot over an esophageal or gastric varices, with no other endo-

scopically observed source of bleeding; (c) presence of large esophageal or gastric varices and blood in the stomach with exclusion of other causes of bleeding (erosive gastropathy or ulcers) at emergency endoscopy and confirmed at early control. Olympus GIF IT-10 or GIF XQ-20 endoscopes were used. At each endoscopic session the size of the esophageal varices was graded according to Beppu et al. classification [1]: grade 1, smaller than 3 mm; grade 2, 4–6 mm; grade 3, 7–10 mm; grade 4, larger than 10 mm or large enough to fill the esophageal lumen completely . Gastric varices were graded according to the criteria proposed by the North Italian Endoscopy Club [31]: F1, large varices but rectilinear; F2, resembling F1 but only mildly tortuous; F3, rectilinear, nodular, and tortuous varices. Based on endoscopic findings and on the decrease in hemoglobin level (to above or below 2 g/dl), the investigators defined the severity of the bleeding as severe or moderate.

Criteria for eligibility were: age over 18 years, no history of former myocardial infarction, no cardiac or renal failure, and no pregnancy. Patients with contraindications to endoscopy, intercurrent illness with death expected within 2 months, or symptoms of esophageal dysfunction were excluded from the study.

Thirty-eight subjects presented with hematemesis, 58 with melena, and 12 with hypovolemic shock. Esophageal varices were the cause of bleeding in 41 patients and gastric varices in 19. Seventeen patients had one or more previous gastrointestinal bleeding episodes, and 15 had undergone previous sclerotherapy treatment in other departments. Informed consent was obtained from each patient or relative, after a detailed explanation of the nature and purpose of the study according to Helsinki declaration.

Trial description

The patients were randomized by a table of random numbers (each number contained in a closed envelope) to receive either octreotide (group A, $n = 30$) or terlypressin (group B, $n = 30$). Patients were blinded to treatment, but clinicians were not. A double-blind study was not possible because of the differing schedules for the two drugs.

Acute treatment (period I, 24 h). On admittance to the intensive care unit all patients had major upper gastrointestinal bleeding. The first therapeutic approach was the immediate start in both groups of vasoactive treatment (group A: octreotide 100 μg bolus followed by the continuous intravenous infusion of 25 μg/h; group B: terlypressin 2 mg bolus every 4 h). At the same time, blood, plasma, plasma expanders, and fluid were administered, based on the clinical condition, to restore stable hemodynamic conditions. The Sengstaken-Blakemore tube was positioned, but the balloon was not inflated unless required by the persistence and the severity of bleeding. The source of bleeding was confirmed by emergency upper gastrointestinal endoscopy performed at an average time of 5.3 h (range 2–6) after admission. The ECG was continuously monitored throughout drug infusion. Blood samples were drawn every hour from cubital vein to check red blood cells, white blood cells, hemoglobin, hematocrit, glycemia, blood ammonia, and urea. At the end of the acute period the patients still bleeding underwent, for ethical reasons, sclerotherapy treatment. Sclerotherapy was performed in all patients by the same endoscopist. The sclerosant used was 1–1.5% polydocanol at the rate of 15–20 ml by intra- and perivariceal multiple injections. All patients continued pharmacological therapy (see below).

Postacute treatment (period II, 2nd–7th day). Group A received octreotide 100 μg t.i.d., administered subcutaneously; group B received terlypressin, 2 mg every 6 h on the 2nd day and then 1 mg every 6 h until the 7th day, given intravenously. The patients received the standard routine management for variceal bleeding; neither specific vasoactive compounds (other than the trial drug) nor antiulcer treatments (including H_2 receptor antagonists) were allowed. Concomitant therapies for disorders unrelated to the trial indication were administered and recorded.

Follow-up. A follow-up period of 2 months started at the end of the period II for all patients: they were checked by clinical and endoscopic examinations on days 7, 15, 30, and 60. During the follow-up sclerotherapy treatment was carried out only in patients showing endoscopic signs of rebleeding. During the whole observation time, possible adverse effects (noxious and unintended reactions) or side effects (effects of the two drugs in addition to their intended function) were recorded.

Definition of control of bleeding and treatment failure

Control of hemorrhage was defined as the cessation of bleeding for at least 12 h consecutively. Cessation of bleeding was defined by the absence of fresh blood in the nasogastric aspirate for 1 h, associated

Table 1. Clinical and laboratory characteristics of 60 patients in octreotide (A) and terlypressin (B) groups.

	Group A ($n=30$)	Group B ($n=30$)	P
Age (years)	64.7 ± 10.7	66.7 ± 10.6	NS*
Sex: male/female	18/12	17/13	NS**
Etiology of cirrhosis			
Alcoholic	11	9	NS**
Posthepatitic			
HCV	14	13	NS**
HBV	5	8	NS**
Child-Pugh grade			
A	4	5	NS**
B	23	21	NS**
C	3	4	NS**
Mean data on admission			
Hemoglobin (g/dl)	8.9 ± 0.8	8.8 ± 0.8	NS*
Hematocrit (%)	26.4 ± 2.2	26.0 ± 4.1	NS*
Sistolic blood pressure (mmHg)	98.6 ± 6.7	97.8 ± 7.3	NS*
Diastolic blood pressure (mmHg)	66.3 ± 6.7	67.4 ± 8.3	NS*
Heart rate (beats/min)	99.6 ± 10.8	102.4 ± 9.2	NS*
Albumin (g/dl)	2.7 ± 0.4	2.6 ± 0.3	NS*
Prothrombin ratio (%)	60.5 ± 8.7	61.4 ± 11.3	NS*

* Student's t test for unpaired data; ** Fisher's exact test

with stabilization of hematocrit and vital signs (i.e., blood pressure and heart rate); this was confirmed by endoscopy performed at the 24th h. Rebleeding was defined as recurrence of bloody emesis or bright red blood in the nasogastric aspirate with a drop in the hemoglobin level of more than 1 g/dl. Treatment failure was defined as the occurrence of each one of the following symptoms: continued bleeding uncontrolled by treatments and requiring blood transfusion; deterioration of vital signs unrelated to other factors.

End-points

The primary end-points of the study were the control of active variceal bleeding and the incidence of recurrent bleeding. Secondary end-points included incidence of complications depending on pharmacological treatment and overall mortality.

Statistical analysis

For calculation of sample size we assumed a bleeding control rate of about 47% with terlypressin and about 75% with octreotide after an intermediate analysis on 30 patients. Of consequence a global number of 30 patients for each group was considered in order to foresee an alpha error of 0.05 and a power of 85%. Data are reported as mean ± SD. Student's t test for unpaired data, the chi-square test for k independent samples, and Fischer's exact test were used for the statistical analysis of the results. For mortality assessment the Kaplan-Meier method was used to construct life tables, and the generalized Savage (Mantel-Cox) test was used to assess differences between the groups.

Results

The clinical and laboratory features of all patients at the time of randomization are reported in Table 1. No statistically significant difference was observed between the two groups in relation to age, sex, etiology of cirrhosis or liver function tests. In addition, there was no difference between the two groups with respect to the Child-Pugh classification [7]; in both groups about 80% of the patients were in class A or B. Table 2 illustrates the endoscopic assessment of bleeding; the two groups were also comparable here.

Control of bleeding

Period I. At the end of the period I (24 h) the hemorrhage was stopped in 23 (76.6%) and in 16 (53.3%) patients in groups A and B, respectively. This difference was not statistically significant. Regarding the anatomical source of the hemorrhage, in group A the bleeding was stopped in 17 of the 21

Table 2. Endoscopic assessment of bleeding in octreotide (A) and terlypressin (B) groups

	Group A ($n=30$)	Group B ($n=30$)	P*
Source of bleeding			
Esophageal varices	21	20	NS
Gastric varices	9	10	NS
Severity of bleeding**			
Severe	17	18	NS
Moderate	13	12	NS
Previous G.I. bleeding			
Yes	8	9	NS
No	22	21	NS
Previous sclerotherapy treatment			
Yes	7	8	NS
No	23	22	NS

* Fischer's exact test; ** Investigators assessment

Table 3. Results of octreotide (group A) and terlypressin (group B) treatment in controlling acute variceal bleeding

	Group A ($n=30$)	Group B ($n=30$)	P*
Primary control of bleeding	23/30 (76.6%)	16/30 (53.3%)	NS
Esophageal varices	17/21 (80.9%)	12/20 (60%)	NS
Gastric varices	6/9 (66.6%)	4/10 (40%)	NS

*Fischer's exact test

patients with esophageal varices (80.9%) and in 6 of 9 with gastric varices (66.6%); in group B complete control of bleeding was obtained in 12 of the 20 patients with esophageal varices (60%) and in 4 of 10 (40%) with gastric varices (Table 3). No statistical correlation was found between acute variceal bleeding and the extent of bleeding (moderate or severe) in the two groups. Primary control of moderate and severe bleeding was effective in 19 of 22 and in 5 of 8 patients in group A (chi square = 2.088, NS) and in 14 of 23 and 2 of 7 (chi square = 2.249, NS) in group B, respectively. The interval between initiation of drug infusion and full control of bleeding was shorter in the patients treated with octreotide (6.3 ± 4.1 h) than in those with terlypressin (8.5 ± 4.5 h) but without statistically significant difference. To achieve a stable hemodynamic condition, the patients of the two groups received on average 1.7 ± 1.4 and 1.8 ± 1.5 blood units (NS) or 1680 ± 755 and 1760 ± 785 ml (NS) of plasma expanders or other fluids (i.e., saline or hypertonic glucose solutions), respectively. The esophageal balloon was inflated after 4 h only in one patient in group A for continuous and massive bleeding. No patient suffered rebleeding during period I in either groups. No correlation between bleeding control and the Child-Pugh classification was observed for either treatments (Table 4).

Period II. Seven patients in group A and 14 in group B still bleeding at the end of the period I underwent the first session of sclerotherapy (Fig. 1). At the end of period II (7th day) 29 patients in group A were alive and free of bleeding vs. 28 in group B. One patient (class C) in group A and two patients (both class C) in group B died within 4 days for hepatorenal syndrome, massive bleeding, and pulmonary complications, respectively.

Follow-up. At the end of the 2 months of follow-up 27 patients in group A and 26 in group B were alive and free of bleeding (Fig. 1). In neither group was there any patient with bleeding controlled by the vasoactive treatment who suffered rebleeding during this period. Two patients in group A and two in group B who underwent scleroteraphy in period II rebled and died for hypovolemic shock and hepatic failure 12–21 days after discontinuation of treatment.

Table 4. Control rate of bleeding with octreotide (group A) and terlypressin (group B) in relation to Child-Pugh classification

	Class[a]	Control (n)	Bleeding (%)	P*	Mortality (n)	P** (A+B vs C)
	A	3/4	75		0	
Group A	B	19/23	82.6	NS	0	
($n=30$)	C	1/3	33.3		3/3	0.001
	A	3/5	60		0	
Group B	B	14/21	66.6	NS	0	
($n=30$)	C	0/4	0		4/4	0.001

[a] Class A: good hepatic function; class B: intermediate hepatic function; class C: poor hepatic funcion (8); * chi-square test for independent samples; ** Fisher's exact test

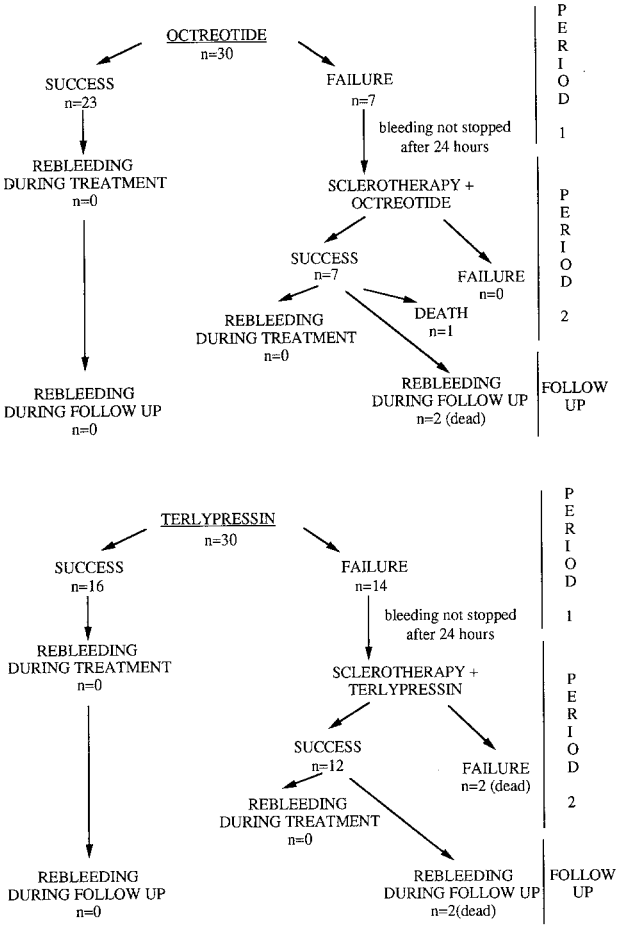

Fig. 1. Outcome of treatment with octreotide and terlypressin in patients with acute variceal hemorrhage. *Period* 1, 24 h; *period* 2, next 6 days; *follow-up*, next 60 days

Table 5. Complications during therapy in octreotide (A) and terlypressin (B) groups

	Group A ($n=30$)	Group B ($n=30$)	P*
N. of patients with complications	7	18	0.01
Adverse effects			
Bradycardia (<50 heart-beats/min)	2	3	NS
Ventricular extrasystoles	1	1	NS
Side effects			
Severe diarrhoea	2	7	NS
ECG ischemia	0	3	NS
Abdominal pain	0	2	NS
Transient hyperglycemia	3	0	NS
Headache	0	2	NS

*Fisher's exact test

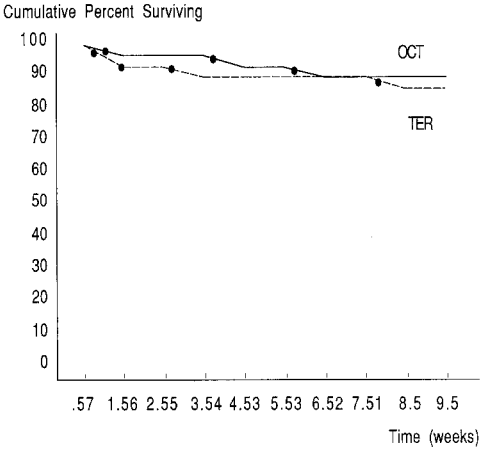

Fig. 2. Kaplan-Meier survival plots of 9.5 weeks for patients randomized to receive octreotide (*OCT*) or terlypressin (*TER*). *Time* 0, time of endoscopy

Complications

None patients experienced adverse or side effects that required withdrawal of treatment during the acute phase or the maintenance period (Table 5). The complication rate was significantly lower ($P < 0.01$) in group A (7 patients, 23.3%) than in group B (19 patients, 63.3%). Adverse reactions such as episodes of bradycardia or ventricular extrasystoles occurred in seven patients: two and one in group A and three and one in group B, respectively. Side effects such as transient severe diarrhea were experienced by two patients in group A and seven in group B in which increased bowel movements were observed in all patients. Among other side effects, transient hyperglicemia was registered in three patients of group A; episodes of abdominal pain, headache, and ECG ischemia in two, two and three patients of group B, respectively. The episodes of ECG ischemia were transient and intercurred without clinical symptoms. The ECG alteration improved spontaneously, and no specific treatment was needed. One patient treated with octreotide showed more than one complication.

Mortality

Overall mortality during the study period was similar in both groups (Fig. 1). Three patients treated with octreotide (10%) and four patients receiving terlypressin (13.3%) died (NS). The Kaplan-Meier 9.5-week survival plots (Fig. 2) were similar for patients treated with octreotide or terlypressin and the difference in the progression rate between the two groups of subjects was not significant (95% confidence intervals: group A 8.21–9.62 weeks; group B 7.72–9.56 weeks). The mortality rate was clearly correlated with the Child-Pugh classification and in both groups was significantly higher in Child C patients (Table 4).

Discussion

Bleeding from esophageal and/or gastric varices is a well-recognized complication of portal hypertension in cirrhotics, associated with 28–65% mortality [20]. It is known that some vasoactive drugs can reduce portal pressure. In experimental studies vasopressin has been shown to induce potent vasoconstriction in the splanchnic circulation decreasing portal blood flow and pressure [2, 25]. This drug has been widely used in several clinical trials in the treatment of variceal bleeding [6, 18, 24]. Nevertheless vasopressin infusion is associated with undesirable side effects such as coronary vasoconstriction, pulmonary edema, and abdominal colic [2]. The action of vasopressin analogue, terlypressin (triglycyllysin vasopressin), a prohormone releasing the active hormone by gradual enzymatic cleavage of terminal aminoacids in vivo [21], on portal blood flow and pressure is more prolonged in time (4–6 h instead of 15–30 min). Several studies have shown a full control of the acute variceal hemorrhage without effect on heart in about 50–80% of treated patients, with less side effects than vasopressin [9–11, 23, 27, 32, 33].

Several uncontrolled and controlled studies have shown that somatostatin infusion can arrest variceal bleeding in cirrhosis [3, 12, 15, 22, 29, 30]. However, large amounts of the natural peptide must be administered by i.v. infusion because of its very short half-life (2–4 min).

To circumvent this limitation, a new synthetic somatostatin analogue, octreotide, with the same biological effect of the native peptide and a much longer half-life (100 min), has recently been proposed [8]. The rationale for using octreotide in the treatment of upper gastrointestinal bleeding is the significant reduction in portal pressure obtained in experimental animal models [13] and in patients with portal hypertension either with intravenous bolus administration or continuous infusion or subcutaneous injection [5, 14, 19]. Some recent randomized clinical studies have shown that the efficacy of octreotide in the control of variceal bleeding is similar to that of sclerotherapy [28] or esophageal tamponade [17].

The present randomized trial was designed to investigate the effects of octreotide and terlypressin in cirrhotic patients during the acute bleeding and the following hospitalization period. Acute variceal bleeding was arrested in 76.6% of patients by octreotide infusion and in 53.3% by terlypressin treatment; the difference between the two groups was not statistically significant. The success rates with octreotide or terlypressin separately considered were similar to those reported in previous controlled studies [26, 28]. Hemorrhage control and stable hemodynamic condition were achieved in a short time in both groups. No significant difference was observed in the time needed to stop the bleeding. Nevertheless, octreotide controlled the hemorrhage more rapidly than terlypressin (6.3 vs. 8.5 h); since clinical outcome and blood transfusion requirements in the two groups were similar, this appears to be less relevant. Therefore the results of the present study suggest that octreotide and terlypressin are equally effective in the acute treatment of variceal bleeding.

The control of rebleeding was achieved with either treatment in all patients: those still bleeding at the end of the acute phase underwent sclerotherapy treatment together with administration of vasoactive drugs. No further bleeding was observed during period II in patients of group A, while two patients continued to bleed in group B even though sclerotherapy had been carried out.

Terlypressin induced a significantly higher number of complications than octreotide, as reported in previous studies (mainly cardiovascular and gastrointestinal [27]). Moreover, the increased bowel movements induced by terlypressin could be considered beneficial in cirrhotic patients with protein intolerance because of the lower intestinal absorption of ammoniagenic compounds. This could explain the higher blood ammonia levels observed in group A than in group B (98.2 ± 27.1 vs. 70.4 ± 27.1; $P < 0.005$, data not shown). Therefore, the lower rate of side effects induced by octreotide could mean a more selective action of this drug on the splanchnic vascular bed [16].

The mortality, strictly related to the degree of impairment of liver function, was higher in Child-Pugh class C than in classes A and B.

In conclusion, the results of this single-blind randomized clinical trial suggest that octreotide is at least as effective as terlypressin as a stop-gap adjuvant therapy, before other treatment (sclerotherapy, transgiugular intravenous porto-systemic shunt) are carried out in bleeding cirrhotics. Both drugs, either alone or associated with sclerotherapy, exert a similar favourable effect also on early rebleeding. Moreover, the involved cost/benefit ratio must be taken into account, since the cost of terlypressin is approximately 6.7 times higher than that of octreotide.

Further investigations on larger populations of patients, possibly by double blind trials, are needed to confirm these observations.

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References

1. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, Kobayashi M (1981) Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc 27:213–218
2. Bosch J, Kravetz D, Rodes J (1981) Effects of somatostatin on hepatic and systemic hemodynamics in patients with cirrhosis of the liver. Comparison with vasopressin. Gastroenterology 80:518–525
3. Burroughs AK, McCormick PA, Spangers D, McIntyre N (1989) Randomized double-blind placebo controlled study of somatostatin for control of variceal bleeding. Gut 29: A1431
4. Burroughs AK, McCormick PA, Hughes MD, Spangers D, D'Heygere F, McIntyre N (1990) Randomized, double-blind, placebo-controlled trial of somatostatin for variceal bleeding. Gastroenterology 99:1388–1394
5. Christiansen J, Ottenjann R, Von Arx F (1989) Placebo-controlled trial with the somatostatin analogue SMS 201–995 in peptic ulcer. Gastroenterology 97:568–574
6. Conn HO, Ransby GR, Storer EH, Mutchnick MG, Joshi PH, Phillips MM, Cohen GA, Fields GN, Petroski D (1975) Intrarterial vasopressin in the treatment of upper gastrointestinal hemorrhage: a prospective controlled clinical trial. Gastroenterology 68:211–221
7. Conn HO (1981) A peek at the Child-Turcotte classification. Hepatology 1:673–676
8. Fiaccadori F, Pedretti G, Biraghi M, Arcidiacono R (1993) Terlypressin and endoscopic sclerotherapy control variceal bleeding and prevent early rebleeding in cirrhotic patients. Curr Ther Res 54:519–528
9. Del Pozo E, Neufeld M, Schluter K, Tortosa F, Clarenbach P (1986) Endocrine profile of a long-acting somatostatin derivate SMS 201–995: study in normal volunteers following subcutaneous administration. Acta Endocrinol 111:433–439
10. Freeman JG, Cobden I, Lishman AH, Record CO (1982) Controlled trial of terlypressin (glypressin) versus vasopressin in the early treatment of oesophageal varices. Lancet II: 66–68
11. Freeman JG, Cobden I, Record CO (1989) Placebo controlled trial of terlypressin (glypressin) in the management of acute variceal bleeding. J Clin Gastroenterol 11:58–60
12. Jenkins SA, Baxter JN, Corbett W, Dewitt P, Ware J, Shields R (1985) A prospective randomized controlled clinical trial comparing somatostatin and vasopressin in controlling acute variceal hemorrhage. Br Med J 290:275–278
13. Jenkins SA, Baxter JN, Corbett WA, Shields R (1985) The effects of somatostatin analogue SMS 201–995 on hepatic hemodynamics in the cirrhotic rat. Br J Surg 72:864–867
14. Jenkins SA, Baxter JN, Ellenbogen S, Shields R (1988) Effects of somatostatin and SMS 201–995 on hepatic and systemic hemodynamics in patients with cirrhosis and portal hypertension. Gut 29: A 720
15. Kravetz D, Bosch J, Teres J, Bruix J, Rimola A, Rodes J (1984) Comparison of intravenous somatostatin and vasopressin infusion in the treatment of acute variceal hemorrhage. Hepatology 4:442–446
16. Lin HC, Tsai YT, Lee FY, Lee SD, Hsia HC, Lin WJ, Lo KJ (1992) Hemodynamic evaluation of octreotide in patients with hepatitis B-related cirrhosis. Gastroenterology 103:229–234
17. McKee R (1990) A study of octreotide in oesophageal varices. Digestion 45 [Suppl 1]:60–65
18. Merigan TC Jr, Plotkin GR, Davidson CS (1962) Effect on intravenously administered posterior pituitary extract of hemorrhage from bleeding esophageal varices. A controlled evaluation. N Engl J Med 266:134–135
19. Navasa M, Bosch J, Chesta J, Bru C, Pizcueta P, Garcia-Pagan JC, Betz C, Casamitjana R, Rodes J (1988) Hemodynamic effects of subcutaneous administration of SMS 201–995, a long acting somatostatin analogue, in patients with cirrhosis and portal hypertension. J Hepatol 7: S64
20. Olsson R (1980) The natural hystory of esophageal varices: a retrospective study of 224 cases with liver cirrhosis. Digestion 6:65–74
21. Pliska V, Chard T, Rudinger J, Forsling ML (1976) In vivo activation of synthetic hormonogens of lysine-vasopressin: *N*-glycyl-glycyl-glycyl-(8-lysine)vasopressin in the cat. Acta Endocrinol 81:474–481
22. Pugh RN, Munnay Lyon IM, Dawson JL, Pietroni MC, Williams R (1973) Transection of the oesophagus for bleeding esophageal varices. Br J Surg 60:646–649
23. Rabol A, Juhl E, Schmidt A, Winkler K (1976) The effect of vasopressin and tryglycyl lysine vasopressin (terlypressin) on the splanchnic in cirrhotic patients with portal hypertension. Digestion 14:285–289
24. Shaldon S, Sherlock S (1960) The use of vasopressin (pitressine) in the control of bleeding from esophageal varices. Lancet II: 222–225
25. Shaldon S, Dolle W, Guevara L, Iber FL, Sherlok S (1961) Effect of pitressin on the splanchnic circulation in man. Circulation 24:797–807
26. Silvain C, Carpentier S, Sautereau S, Sautereau D, Czernichow B, Metreau JM, Fort E, Ingrand P, Boyer J, Pillegand B, Doffel M, Dhumeaux D, Beauchant M (1993) Terlypressin plus transdermal nitroglycerin vs. octreotide in the control of acute bleeding from esophageal varices: a multicenter randomized trial. Hepatology 18:61–65
27. Soderlund C, Magnusson I, Tongfen S, Lundell L (1990) Terlypressin controls acute bleeding oesophageal varices: a double-blind, randomised placebo-controlled trial. Scand J Gastroenterol 25:622–630
28. Sung JJY, Chung SCS, Lai CW, Chan FKL, Leung JWC, Yung MY, Kassianides C, Li AKC (1993) Octreotide infusion or emergency sclerotherapy for variceal hemorrhage. Lancet 342:637–641
29. Terblanche J, Burroughs AK, Hobbs KEF (1989) Controversies in the management of bleeding esophageal varices. N Engl J Med 320:1393–1398
30. Testoni PA, Masci E, Passaretti A (1986) Comparison of somatostatin and cimetidine in the treatment of acute bleeding esophageal varices. Curr Ther Res 39:758–761
31. The North Italian Endoscopic Club (1987) Protocolli di valutazione endoscopica, definizioni acquisite e proposta di nuove definizioni. Procedings, I Convegno Nazionale NIEC 1984
32. Vosmik J, Jedlicka K, Muldler J, Cort JH (1977) Action of triglycyl hormonogen of vasopressin (glypressin) in patients with liver cirrhosis and bleeding esophageal varices. Gastroenterology 72:605–609
33. Walker S, Stiehl A, Reedsch R, Kommerell B (1986) Terlypressin in bleeding oesophageal varices: a placebo controlled, double-blind study. Hepatology 6:112–115