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Effectiveness of Adjunctive Drug Therapy to Endoscopic Stenting in Liver Cirrhosis Complicated by Refractory Variceal Bleeding

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AIM OF THE STUDY Comparative clinical analysis of the efficacy of terlipressin and octreotide as additional drug therapy to mechanical hemostasis with nitinol stent in patients with liver cirrhosis complicated by bleeding from esophageal varices refractory to endoscopic treatment.

MATERIAL AND METHODS

Thirty-one patients with liver cirrhosis complicated by esophageal variceal bleeding refractory to endoscopic treatment, in whose complex treatment program, as a first-line life-saving measure, hemostasis with a self-expanding hemostasis was performed nitinol stent were randomly assigned to two groups. In group A, 20 patients were treated with terlipressin as an adjuvant to mechanical hemostasis, and in group B, 11 patients were treated with octreotide. Unpaired Student's t -test was used for statistical analysis of the results. Graphs for assessing the survival function of patients for 8 weeks after the end of treatment were constructed using the Kaplan-Meier method.

RESULTS In the acute observation period terlipressin and octreotide were equally effective in treating refractory variceal bleeding. In the subacute observation period, the administration of octreotide was generally accompanied by a greater number of side effects (54.5%) than terlipressin (30.0%) (p=0.453). In the remote observation period, 8-week survival in the group of patients receiving terlipressin was higher than in the group of patients receiving octreotide.

CONCLUSION Terlipressin is as effective as octreotide as an adjunct to endoscopic stenting in drug therapy for liver cirrhosis complicated by esophageal variceal bleeding refractory to endoscopic treatment.

At the same time, terlipressin has a greater effect than octreotide on reducing 8-week mortality, which approaches statistical significance. In this regard, terlipressin may be the vasoactive drug of choice in acute refractory variceal bleeding.

Keywords: portal hypertension, refractory variceal bleeding, endoscopic stenting, drug therapy, vasoactive drugs

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INTRODUCTION

In 15–20% of patients with cirrhosis and esophageal varices, primary massive bleeding either cannot be managed by endoscopic ligation or relapses within the next 5 days [1, 2]. Mortality in such patients reaches 30–50% [3]. Such bleeding, refractory to endoscopic treatment, requires a combination of endoscopic stenting and additional drug therapy with vasoactive drugs in the treatment program [4–8].

Among the drugs that cause splanchnic vasoconstriction, a decrease in portal blood flow and pressure in the portal venous system, the vasopressin analogue N-Triglycyl-8-lysine-vasopressin acetate (terlipressin) and the synthetic analogue of somatostatin (octreotide) have been proposed and widely used in recent years with a successful hemostatic effect [9]. However, the choice of drugs for additional drug therapy for refractory variceal bleeding remains controversial [10].

The aim of the randomized clinical study was a comparative clinical analysis of the effectiveness of terlipressin and octreotide as additional drug therapy to mechanical hemostasis with a nitinol stent in patients with liver cirrhosis complicated by bleeding from esophageal varices refractory to endoscopic treatment.

MATERIAL AND METHODS

The study included 31 patients with liver cirrhosis complicated by bleeding from esophageal varices refractory to endoscopic treatment, in whose complex treatment program hemostasis with a self-expanding nitinol stent was performed as a life-saving first-line measure. The inclusion criteria for tamponade with a self-expanding nitinol stent were bleeding that recurred within 2 hours after endoscopic ligation, or massive bleeding, the severity of which excluded endoscopic ligation, or the latter was technically unavailable to us at the time of bleeding [11].

All patients were then randomly assigned to two groups. In group *A*, 20 patients were given terlipressin at a dose of 1.0 mg as an adjuvant to mechanical hemostasis, first intravenously (IV) as a bolus and then IV by drip at 6-hour intervals. In group *B*, 11 patients were given octreotide at a dose of 200 mcg IV by drip at a rate of 25 mcg/h.

For statistical analysis of the results, the unpaired Student's *t* -test of independent samples was used [12]. Frequency (α) = 0.05. Graphs for assessing the survival function of patients for 8 weeks after the end of treatment were constructed using the Kaplan-Meier method [13].

The clinical characteristics of all patients at the time of randomization are presented in Table 1.

Laboratory characteristics of all patients at the time of randomization are presented in Table 2.

The source of bleeding was confirmed by emergency upper gastrointestinal endoscopy performed within 2 hours of admission. Table 3 illustrates the endoscopic findings in our patients.

Table 1

Clinical characteristics of patients upon admission

Indicator	Group *A* terlipressin (*n*=20)		Group *B* octreotide (*n*=11)		Total (*n* =31)	
	Abs. number	%	Abs. number	%	Abs. number	%
Floor						
Men	8	40.0	4	36.4	12	38.7
Women	12	60.0	7	63.6	19	61.3
Age (in years)						
From 15 to 39 years old	3	15.0	2	18.2	5	16.1
From 40 to 59 years old	13	65.0	6	54.5	19	61.3
From 60 and above	4	20.0	3	27.3	7	22.6
Etiological factors of liver cirrhosis						
Viral hepatitis *B*	3	15.0	1	9.1	4	12.9
Viral hepatitis *C*	8	40.0	5	45.5	13	41.9
Mixed hepatitis *B* and *C*	3	15.0	-	-	3	9.7
Autoimmune hepatitis	1	5.0	1	9.1	2	6.5
Alcoholic cirrhosis	5	25.0	4	36.4	9	29.0
Degree of cirrhosis compensation according to *Child–Pugh criteria*						
Class *A*	2	10.0	1	9.1	3	9.7
Class *B*	13	65.0	6	54.5	19	61.3
Class *C*	5	25.0	4	36.4	9	29.0
Activity of liver cirrhosis						
Inactive	7	35.0	4	36.4	11	35.5
Low activity	12	60.0	6	54.5	18	58.1
Highly active	1	5.0	1	9.1	2	6.4
Severity of blood loss according to the classification of A.I. Gorbashko (1974)						
Easy	1	5.0	–	–	1	3.2
Average	11	55.0	3	27.3	14	45.2
Heavy	8	40.0	8	72.7	16	51.6
Blood pressure						
Systolic, mmHg	97.3±7.1	–	98.1±6.3	–	97.5±6.9	–
Diastolic, mmHg	61.0±8.2	–	68.0±6.8	–	64.8±7.1	–
Pulse rate, bpm	112.8±17.1	–	108.4±21.6	–	110.9±19.8	–

Table 2

Laboratory parameters of patients upon admission

Indicator	Reference values	Group *A* terlipressin (*n*=20)	Group *B* octreotide (*n*=11)	*p-value*
Hemoglobin, g/l	120–160	82.7±23.1	83.1±21.8	0.319
Hematocrit, %	36–48	26.1±2.1	26.8±3.2	0.246
Erythrocytes, $\times 10^{12}$/l	3.7–5.1	2.3±0.1	2.1±0.3	0.716
Platelets, $\times 10^{9}$/l	150–350	121.3±55.8	119.5±67.1	0.335
Aspartate aminotransferase, U/l	31–37	42.7±11.4	40.3±12.1	0.399
Alanine aminotransferase, U/l	34–45	49.3±13.1	48.8±11.5	0.339
Total bilirubin, μmol/l	0–21	45.1±2.1	49.6±3.1	0.352
Prothrombin index, %	70–100	56.0±13.2	53.9±11.4	0.386
Serum albumin, g/l	35–52	30.9±0.9	31.4±0.7	0,160

Table 3

Endoscopic characteristics of patients in the study groups

	Group A terlipressin (n=20)		Group B octreotide (n=11)		*p-value*
	Abs. number	%	Abs. number	%	
Varicose veins of the esophagus according to A.G. Shertsinger (1986)					
Grade I - vein diameter up to 3 mm	–	–	–	–	–
II degree - vein diameter from 3 to 5 mm	6	30.0	3	27.3	0.50
Grade III - vein diameter greater than 5 mm	14	70.0	8	72.7	0.21
History of bleeding episode					
Yes	13	65.0	8	72.7	0.11
No	7	35.0	3	27.3	0.16
History of Sengstaken-Blakemore tube placement					
Yes	20	100,0	11	100,0	0.30
No	–	–	–	–	–
History of endoscopic ligation					
Yes	20	100,0	11	100,0	0.30
No	–	–	–	–	–

Diagnostic esophagogastroduodenoscopy revealed either active bleeding from esophageal varices or varices with evidence of recent bleeding.

Thus, both groups were comparable with respect to age, gender, etiology of cirrhosis and liver function tests. There was also no statistically significant difference in endoscopic bleeding scores.

ACUTE OBSERVATION PERIOD (1ST day)

Self-expanding nitinol stent is a hollow metal frame made of nitinol wire covered with a silicone film [14]. The diameter of the expanded stent is 25 mm, the diameter of the neck is 30 mm, the length of the stent is 135 cm (Fig. 1). After installation, the distal end of the stent should be located 1–2 cm below the esophagogastric junction, and the proximal end should be below the upper esophageal sphincter (Fig. 2).

Fig. 1. The view of the self-expanding nitinol stent in expanded state

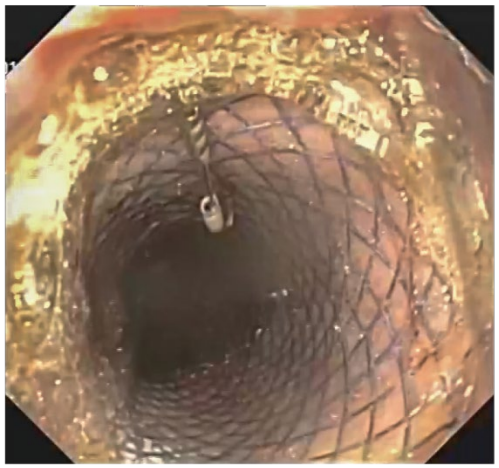

Fig. 2. Endoscopic picture. Self-expanding nitinol stent in standard position in the esophagus

As adjuvants to mechanical hemostasis in 20 patients (group *A*), terlipressin was used at a dose of 1.0 mg, first intravenously by bolus, and then intravenously by drip at 6-hour intervals, and in 11 patients (group *B*), octreotide was used at a dose of 200 mcg intravenously by drip at a rate of 25 mcg/h. At the same time, based on the clinical condition, in both groups, single-group red blood cell mass, plasma, hemodynamic plasma substitutes and regulators of water-salt and acid-base metabolism were administered to restore stable hemodynamic parameters. Cessation of bleeding was determined by the absence of fresh blood intake for 6 hours, stabilization of hemodynamic and laboratory parameters. Relapse of bleeding was defined as the repeated appearance of bloody vomiting with a decrease in laboratory parameters of red blood within 24 hours from the beginning of treatment.

SUBACUTE OBSERVATION PERIOD (2–6 days)

As adjuvants to mechanical hemostasis in the following 5 days, 20 patients of group *A* continued to use terlipressin at a dose of 1.0 mg intravenously by drip at intervals of 6 hours, and 11 patients of group B received octreotide at a dose of 200 mcg intravenously by drip at a rate of 25 mcg/h. Otherwise, patients of both groups received standard drug therapy generally accepted for varicose bleeding. No other specific vasoactive drugs, except those studied, were prescribed.

Bleeding was considered controlled by the study drug if it stopped and a period of at least 24 hours passed without any evidence of repeated bleeding. Treatment was considered unsuccessful if repeated bleeding occurred more than 24 hours after initial hemostasis.

REMOTE OBSERVATION PERIOD (2 MONTHS AFTER DISCHARGE)

Between 30 and 60 days after discharge from the hospital, patients underwent a follow-up clinical and endoscopic examination, during which time possible side effects or complications were recorded.

The effectiveness of pharmacological treatment was determined by the cessation of active variceal bleeding, the frequency of recurrent bleeding, the frequency of side effects and mortality.

RESULTS

ACUTE OBSERVATION PERIOD

As follows from the analysis of the results presented in Table 4, by the end of 24 hours of observation, bleeding was stopped in 17 of 20 patients (85.0%) in group *A* and in 8 of 11 (72.7%) in group *B*. This difference was not statistically significant ($p = 0.943$).

In patients of classes *A* and *B* in both groups, bleeding was stopped in 100% of clinical observations ($p = 0.845$ for class *A* and $p = 0.100$ for class *B*). In patients of class *C,* bleeding was stopped in group *A* in 40%, in group *B* - in 25% of clinical observations ($p = 0.845$).

Table 4

Efficacy of hemostasis in the study groups

	Child–Pugh Class	Total	Termination bleeding		*p-value*	Recurrent bleeding		*p-value*	Re-bleeding		*p-value*
			Abs. number	%		Abs. number	%		Abs. number	%	
Group *A* terlipressin (*n*=20)	*A*	2	2	100	0.845	–	0	–	–	0	–
	B	13	3	100	0.100	–	0	–	2	15.4	0.152
	C	5	2	40	0.845	3	60	0.745	1	20	0.865
	Total	20	17	85	0.943	3	15	0.745	3	15	0.799
Group *B* octreotide (*n*=11)	*A*	1	1	100	0.845	–	0	–	–	0	–
	B	6	6	100	0.100	–	0	–	1	16.7	0.152
	C	4	1	25	0.845	3	75	0.745	1	25	0.865
	Total	11	8	72.7	0.943	3	27.3	0.745	2	18.2	0.799

The time in hours from the start of drug administration to clinical cessation of bleeding was shorter in patients receiving terlipressin (4.3±2.1) than in patients receiving octreotide (6.1±4.5). This difference was not statistically significant ($p = 0.132$).

To achieve a stable hemodynamic state, patients in the two groups received an average of 2.3±1.2 and 2.8±1.4 units of red blood cell mass and 1,100.0±255.0 and 1,125.0±285.0 ml of fresh frozen plasma, respectively.

In 3 (15.0%) patients (all Child–Pugh class C*) of* group *A* and 3 (27.3%) patients (all *Child–Pugh class C*) of group B *,* recurrent bleeding occurred during the acute observation period ($p = 0.745$).

SUBACUTE OBSERVATION PERIOD

In 3 patients (15%) of group *A* and in 2 patients (18.2%) of group B, recurrent bleeding occurred during the subacute observation period ($p = 0.799$). In class *A patients* , there was no recurrent bleeding in either group. In class *B patients,* recurrent bleeding occurred in 15.4% of group *A and in 16.7% of group B* clinical observations ($p = 0.152$). In class *C patients*, recurrent bleeding occurred in 20% of group *A* and in 25% of group *B* clinical observations ($p = 0.865$).

By the end of the 6th day, 15 patients (75%) in group A *were* alive; versus 7 (63.6%) in group *B.*

Five patients (4 Child–Pugh class *C and 1* Child – *Pugh* class *B*) in group *A* and 4 patients (3 Child–Pugh class *C* and 1 Child–Pugh class B*) in* group *B* died within 5 days. Of these, 3 patients (15.0%) (all Child–Pugh class C*) in* group *A* and 3 patients (27.3%) (all Child–Pugh class C*) in* group *B* died of severe blood loss at the peak of repeated bleeding. Two patients (10.0%) (1 Child–Pugh class *C and 1 Child–Pugh* class *B*) in group A *and* 1 patient (9.1%) (Child–Pugh class B*) in* group *B* died of hepatic coma, despite the achieved hemostasis, without an episode of repeated bleeding.

REMOTE OBSERVATION PERIOD

By the end of the second month of observation, 13 patients (65.0%) in group *A* and 5 (45.5%) in group *B* were alive and had no bleeding.

During this period, 3 (15.0%) patients (1 Child–Pugh class C *and* 2 *Child–Pugh class B) in group A and 2 (18.2%)* patients (1 Child–Pugh class *C* and 1 Child–Pugh class B *) in* group B experienced recurrent bleeding ($p = 0.799$). All of them were therefore readmitted. Of these, 2 (10.0%) patients (1 Child–Pugh class *C and 1* Child –*Pugh* class *B*) in group *A* and 2 (18.2%) patients (1 Child–Pugh class *C and 1* Child –*Pugh* class *B*) in group *B* died during readmission from hypovolemic shock and liver failure 28–45 days after stopping treatment during the first hospitalization.

COMPLICATIONS

None of the patients developed complications that required discontinuation of treatment in the acute and subacute periods of observation. As for the side effects of drug therapy, as follows from Table 5, their frequency was lower in group *A* (6 patients, 30.0%) than in group *B* (6 patients, 54.5%) ($p = 0.453$).

Table 5

Side effects of drug therapy in the study groups

Name	Group A terlipressin (*n* =20)		Group B octreotide (*n* = 11)		*p-value*
	Abs. number	%	Abs. number	%	
Number of patients with side effects	6	30.0	6	54.5	0.453
Increased blood pressure	2	10.0	1	9.1	0.392
Bradycardia (<50 beats/min)	2	10.0	2	18.2	0.453
Ventricular extra - systoles	1	5.0	1	9.1	0.453
Transient diarrhea	3	15.0	1	9.1	0.423
Ischemia on ECG	2	10.0	1	9.1	0.392
Abdominal pain	2	10.0	1	9.1	0.392
Transient hyperglycemia	0	0	3	27.3	0.413
Headache	2	10.0	1	9.1	0.392

More than one complication was observed in all 6 patients (30.0%) in group *A* and 6 patients (54.5%) in group *B* ($p = 0.453$).

Thus, the conducted analysis of statistical significance of differences in mean values using Student's *t*-test showed that for all parameters *p-value* was greater than α. Thus, we can accept the null hypothesis as true, namely, that identical indicators in two groups of subjects taking different drugs were approximately equal. In other words, in our clinical material, the drugs had approximately the same therapeutic effect.

MORTALITY

During the entire observation period, 13 patients (41.9%) died, including 7 (35.0%) in group *A* and 6 (54.5%) in group *B* (p = 0.567). In the subacute observation period, 5 patients (25.0%) (all Child–Pugh class C*) in* group *A* and 4 patients (36.4%) (3 Child–Pugh class *C* and 1 Child–Pugh class B*) in* group *B died* (p = 0.555). In the late observation period, 2 (10.0%) (1 Child–Pugh class *C and 1* Child – *Pugh* class *B*) patients in group *A* and 2 (18.2%) (both Child–Pugh class C*) patients* in group *B died* (p = 0.533). The causes of death are presented in Table 6.

Kaplan-Meier plots of 8-week survival for all study groups clearly indicate that survival of patients in group *A* who received terlipressin was higher than survival of patients in group *B* who received octreotide (Fig. 3).

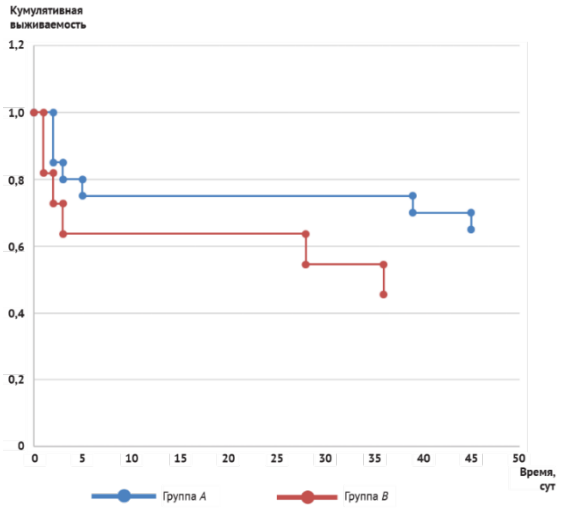

Fig. 3. Kaplan-Meier curves of 8-week survival of all patients in groups A and B

Table 6

Causes of death in the study groups

	Group A, terlipressin (*n* =20)							Group B, octreotide (*n* = 11)					
Age	52	41	35	56	62	58	38	37	57	35	68	42	55
Age	F	M	M	F	F	F	M	M	F	M	F	M	F
Class *B Child–Pugh*					Yes		Yes				Yes		Yes
Class *C Child–Pugh*	Yes	Yes	Yes	Yes		Yes		Yes	Yes	Yes		Yes	
Primary hemostasis				Yes	Yes						Yes		
Recurrent bleeding	Yes	Yes	Yes					Yes	Yes	Yes			
Re-bleeding						Yes	Yes					Yes	Yes
Death (day)	2	2	2	3	5	39	45	1	1	2	3	28	36
Cause of death	Recurrent variceal bleeding	Recurrent variceal bleeding	Recurrent variceal bleeding	Hepatic coma	Hepatic coma	Hypovolemic shock	Hepatic coma	Recurrent variceal bleeding	Recurrent variceal bleeding	Recurrent variceal bleeding	Hepatic coma	Hepatic coma	Hepatic coma

The mortality rate correlated with the level of cirrhosis compensation according to the *Child–Pugh classification*. Kaplan–Meier plots of 8-week survival by cirrhosis class convincingly indicate that in both groups, the survival of class *B patients* was higher than the survival of class *C patients* (Figs. 4 and 5).

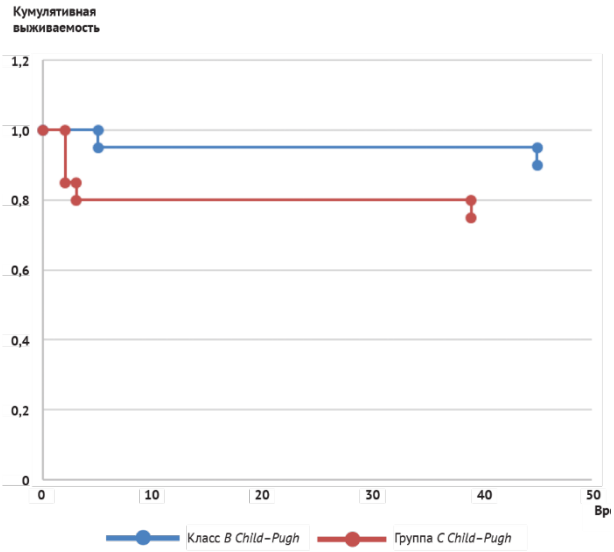

Fig. 4. Kaplan-Meier curves of 8-week survival of patients in group A by Child - Pugh cirrhosis classes

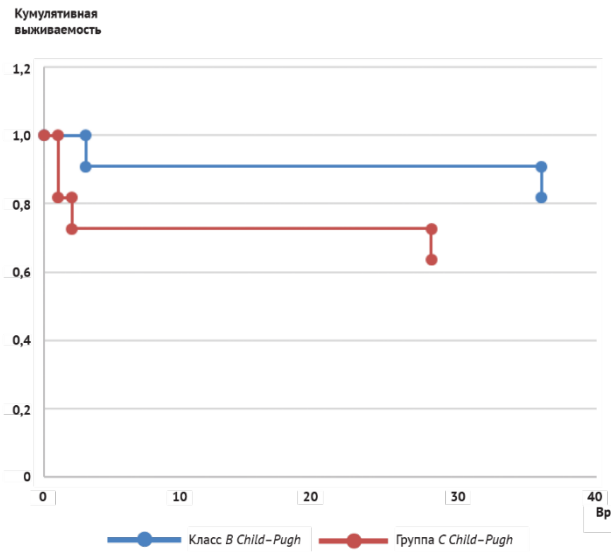

Fig. 5. Kaplan-Meier curves of 8-week survival of patients in group B by Child - Pugh cirrhosis classes

DISCUSSION

Based on the postulate that the goal of treatment of variceal bleeding due to portal hypertension should be aimed at reducing portal pressure, of all potential treatment methods, the administration of vasoactive drugs in combination with endoscopic hemostasis should be initiated as soon as possible and continued for the next 5 days [15]. Continuous progress in understanding the pathophysiology of portal hypertension leads to a gradual expansion of the spectrum of drugs that cause splanchnic vasoconstriction and are potentially suitable for clinical practice [16, 17]. However, when choosing vasoactive drugs that are generally effective and safe in the fight against common acute variceal bleeding, there is considerable controversy in variceal bleeding refractory to endoscopic therapy, since the evidence of efficacy is not equal for each of them [18–21].

Terlipressin, a synthetic analogue of vasopressin, according to a number of authors of several clinical studies, by causing vasoconstriction in the splanchnic circulation and reducing portal blood flow and pressure, has a longer biological activity and significantly fewer side effects and affects the reduction of mortality in 50-80% of treated patients [22, 23]. The rationale for using the synthetic analogue of somatostatin - octreotide in the treatment of variceal bleeding is a significant decrease in portal pressure, obtained both in experimental animal models and in numerous clinical uncontrolled and controlled studies [24, 25].

In this randomized clinical trial, we studied the efficacy of two vasoactive drugs, terlipressin and octreotide, as additional drug therapy in patients with liver cirrhosis complicated by esophageal variceal bleeding refractory to endoscopic treatment, in whose complex treatment program, as a first-line life-saving measure, hemostasis was performed with a self-expanding nitinol stent. In our opinion, in such a clinical situation, it is no less effective and safer option than balloon tamponade.

In accordance with the recommendations of the updated consensus in the field of portal hypertension *Baveno* VII, treatment failure was defined as either lack of hemostasis, or recurrent bleeding within 24 hours from the start of treatment, or recurrent bleeding within the first 5 days of hospital stay. The primary endpoint for the treatment of variceal bleeding was death within 8 weeks after discharge [15].

Acute variceal bleeding was stopped in 17 of 20 patients (85.0%) with terlipressin infusion and in 8 of 11 (72.7%) with octreotide. The difference between the two groups was not statistically significant (p = 0.943). The results obtained with the use of terlipressin or octreotide in variceal bleeding refractory to endoscopic therapy were similar to the results in conventional variceal bleeding obtained in previous controlled studies [26].

In the acute period of observation, hemostasis and stable hemodynamic state were achieved in a short time in both groups. No significant difference in the time required to stop bleeding was observed. However, hemostasis occurred faster with terlipressin than with octreotide (4.3±2.1 versus 6.1±4.5 hours). This difference was not statistically significant (p = 0.132). Thus, the results of this study allow us to assume that both terlipressin and octreotide are equally effective in the treatment of acute refractory variceal bleeding.

In the subacute period of observation, despite the tamponade with self-expanding nitinol stents, recurrent bleeding occurred in 3 patients (15%) against the background of terlipressin infusion and in 2 patients (18.2%) with octreotide (p = 0.799). In general, the introduction of octreotide was accompanied by a greater number of side effects (54.5%) than terlipressin (30.0%) (p = 0.453). In our opinion, the lower frequency of side effects caused by terlipressin may indicate a more selective effect of this drug on the portal vascular bed. At the same time, increased bowel emptying caused by terlipressin in 15.0% of clinical observations in patients with liver cirrhosis can probably be considered useful for reducing the absorption of ammonium compounds in the intestine [9].

In the long-term observation period, recurrent bleeding occurred in 3 patients (15.0%) receiving terlipressin and in 2 (18.2%) receiving octreotide (p = 0.799).

Regarding 8-week survival, in our clinical observations in the group of patients receiving terlipressin it was higher than in the group of patients receiving octreotide.

CONCLUSION

Terlipressin may be the vasoactive agent of choice for acute refractory variceal bleeding. The results obtained with terlipressin or octreotide in variceal bleeding refractory to endoscopic therapy are similar to the results in routine variceal bleeding obtained in previous controlled studies. Further studies are needed to identify potential differences in mortality between terlipressin and octreotide in the setting of adjuvant endoscopic therapy.

CONCLUSIONS

1. Terlipressin is at least as effective as octreotide as an adjunct to endoscopic stenting in medical therapy for liver cirrhosis complicated by esophageal variceal bleeding refractory to endoscopic treatment. This is evidenced by the absence of statistically significant differences between the two studied groups in the acute observation period in the number of patients whose bleeding was stopped (17 out of 20 (85.0%) with terlipressin infusion and 8 out of 11 (72.7%) with octreotide (p = 0.943) and the time to achieve hemostasis (4.3 ± 2.1 versus 6.1 ± 4.5 hours (p = 0.132). In the subacute and late periods - in the number of repeated bleeding (in 3 (15%) with terlipressin infusion and in 2 (18.2%) with octreotide (p = 0.799).

2. Terlipressin has a greater effect than octreotide in reducing eight-week mortality, which approaches statistical significance. This is clearly demonstrated by the Kaplan-Meier plots of 8-week survival in both groups studied.

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