Terlipressin Use in the Emergency Treatment of Patients with Variceal Bleeding in Hepatic Cirrhosis

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Background: Treatment of variceal rupture from portal hypertension remains a therapeutic problem with implications and socio-economic challenge, still insufficient crystallized from a practical point of view, therefore, we considered it necessary to research new therapeutic options.
Methods: We conducted a single center non-interventional observational study on a group of 20 patients in the 2010–2011 period, with the diagnosis of esophageal varices in portal hypertension. We analyzed cases based on physical and laboratory examinations collected from observation sheets, intraoperatory or endoscopic examination, terlipressin efficiency being quantified postterapeutically.
Results: Out of the 20 patients, 75% had ethanol cirrhosis, while a viral etiology was recognized in 25% of cases, class Child-Pugh A and B being the most common. Control of bleeding was achieved in 85% of cases within 12 hours, in 10% of cases the bleeding stopped at intervals over 12 h after the first administration, and only in one case the bleeding persisted despite therapy with terlipressin.
Conclusions: Use of terlipressin is an important option in obtaining hemostasis of upper gastrointestinal bleeding due to variceal rupture. Pharmacologic therapy with terlipressin can save cirrhotic patients with severe or moderate bleeding, requiring transfusion with two units.

Keywords: terlipressin, variceal bleeding, recurrent bleeding

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Introduction

Terlipressin (triglycyl lysine vasopressin) is a synthetic analogue of vasopressin used in the treatment of acute bleeding from ruptured esophageal varices. This hemorrhagic accident is associated with hospital mortality between 20–50%, often in the first 24 hours [1]. Dramatic reduction in mortality in these cases was demonstrated by several authors, who highlighted the bioavailability of terlipressin, which may be administered intravenously at intervals of 4–6 h; compared with vasopressin, terlipressin has no role in plasminogen activation and thus is accompanied by fewer side effects [1–5].

The treatment of variceal rupture from portal hypertension remains a therapeutic problem with implications and a socio-economic challenge, still insufficiently crystallized from a practical point of view, therefore, we considered it necessary to research new therapeutic options. Surgeons, gastroenterologists and anesthesiologists should be closer to the critically ill cirrhotic pacient, in a full bleeding episode, anf terlipressin may be the binder that improves therapeutic outcome in these patients.

The objective of the study is to evaluate the effectiveness of terlipressin in active haemorrhage from oesophageal varices in patients with hepatic cirrhosis of different etiologies, who experienced at least one hemoragic episode.

Material and method

We conducted a single center non-interventional observational study on a group of 20 patients (n=20) admitted to Surgery Clinics 1 and 2, Anesthesia and Intensive Care Clinic 1 and Gastroenterology Clinics 1 and 2 of the County Emergency Clinical Hospital of Târgu Mureș in the January 2010 – December 2011 period, with a diagnosis of esophageal varices in portal hypertension. We analyzed cases based on physical and laboratory examinations collected from observation sheets, intraoperatory or endoscopic examination, terlipressin efficiency being quantified postherapeutically. Each patient was monitored under a special protocol, their written consent being recorded on signature before taking the drug. They met all conditions of EU professional ethics, the patients' identity being secret.

Terlipressin was used as:

a) first pharmacological measure;
b) associated with endoscopic treatment;
c) associated with surgical treatment;
d) associated with mechanical methods (Sengstaken-Blakemore probe tamponament).

The inclusion criteria correspond to the ones layed out in the "Tracking the clinical efficacy of terlipressin in the treatment of bleeding caused by oesophageal varices rupture" project, carried out between 2010–2011 in partnership with the University of Medicine and Pharmacy of Târgu Mureș. These are the following:

a) patients between 18–70 years, hospitalized in the County Emergency Clinical Hospital of Târgu Mureș;
b) patients with cirrhosis;
c) patients with endoscopically confirmed esophageal varices and active or temporarily stopped bleeding.

Each case has been carefully monitored and mapped, completing the follow-up protocol for patients, evalu-

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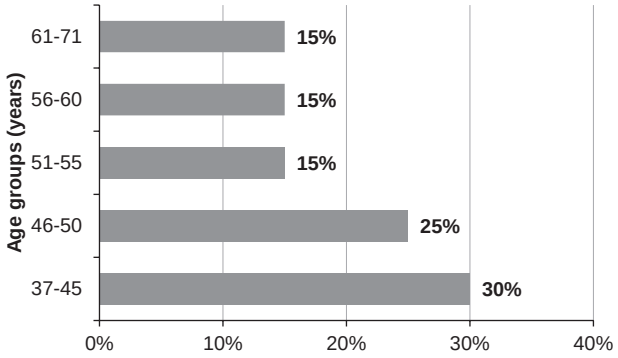

Fig. 1. Distribution of cases according to age

ating the presence of mortality, effectiveness of initial hemostasis, recurrent bleeding, bleeding therapy procedures associated with uncontrolled or recurrent bleeding, amount of blood and blood products administered during hospitalization.

Data were processed in Excel, and statistical analysis was performed with the program Medcalc. We used statistical methods such as descriptive and analytic-inferential methods. We used multivariate analysis (multivariate regression) to determine the relative contributions of different causes to a single event. A p value below 0.05 was considered to be statistically significant.

Results

Out of the 20 patients included in the study, 75% had ethanol cirrhosis, while viral etiology was recognized in 25% of cases, class Child-Pugh A and B being the most common (Table I).

More than half of the cases were young (37–55 years), socio-economically active adults (Figure 1). Most of the patients were males (85%).

According to the Orfanidi classification, small hemorrhages (Htc >35%) accounted for half of the cases, but there were a large number of medium (n=4), large (n=3) or severe hemorrhages (n=3) (Table II).

Bleeding control was achieved in 85% of cases within 12 hours, in 10% of cases the haemorrhage stopped at intervals over 12 h after the first administration and in only one case the bleeding persisted, despite therapy with terlipressin. No recurrent bleeding was observed (Table III).

Table I. Distribution according to diagnosis and Child-Pugh classification

Diagnosis	n	%	Child-Pugh		
			A	B	C
B viral cirrhosis	3	15%	1	2	0
C viral cirrhosis	2	10%	2	0	0
Ethanolic cirrhosis	15	75%	13	1	1
Total	20				

Table II. Orfanidi classification

		n	%
Small	Ht >35 %	11	55%
Medium	Ht 25–35%	4	20%
High	Ht <25%	3	15%
Severe	Ht <15%	2	10%
Total		20	100%

Side effects were minimal (palor and rash). There was one death (5%) in a patient aged 57 years, who presented hepato-renal failure.

The entire group received blood and blood product transfusions (minimum 1–2 units). In patients to whom terlipressin was administered as a prophylactic measure or as an adjuvant to endoscopic therapy, the administration of a single vial before the procedure was sufficient.

Mapping of each case required a subjective assessment of the safety profile and therapeutic efficiency in obtaining hemostasis with terlipressin; in 80% of these cases were positive.

Multivariate regression was used to track how haemorrhage control under 12h is influenced by several factors. The data analysis shows no statistical significance (Table IV).

Discussions

Terlipressin shows a small number of adverse effects and a longer half-life than other vasoactive agents (vasopressin, somatostatin), allowing its use in bolus and even in the suspicion of variceal bleeding [6]. Its use may be ideal in the prevention of primary and secondary variceal bleeding, as noticed in randomized trials [1]. The association of endoscopic (ligation, variceal sclerosis) or surgical therapy (azygo-portal disconnection) improves the prognosis of a hemodynamically stable patient temporized in advance

Table III. Bleeding control and the number of vials administered

	Admission		Under 12 hours		12–24 hours		More than 24 hours	
	n=27	%	n=25	%	n=72	%	n=126	%
Vials administered	1 v – 13 2 v – 7	65 35	1 v – 15 2 v – 5	75 25	2 v – 5 3 v – 6 4 v – 7 6 v – 1 10 v – 1	25 30 35 5 5	4 v – 4 5 v – 5 6 v – 2 7 v – 4 8 v – 4 13 v –1	20 25 10 20 20 5
Hemostasis rate	19	95	19	95	19	95	19	95
Recurrent bleeding rate	–	–	1	5	1	5	1	5

Table IV. Bleeding control under 12 h – multivariate regression

Variables	Coefficient	Std. Error	t	P value
Age	0.009	0.007	1.316	0.21
Sex	0.019	0.208	0.090	0.92
Child-Pugh score	-0.080	0.093	-0.868	0.40
Death	0.004	0.315	0.014	0.98
Transfusion under 12 h	0.218	0.119	1.828	0.78
Dose of terlipressin	-0.167	0.164	-1.020	0.32
Hematocrit	-0	0.007	-0.135	0.89

with terlipressin [6]. In our cases 50% of the patients benefited from a combined treatment (endoscopic and pharmacological) and one patient was subjected to Sugiura-Futagawa type azygo-portal disconnection associated with terlipressin therapy.

We consider that the limited number of cases included in this group does not allow a statistically significant appreciation, but it does encourage the use of terlipressin in variceal bleeding and recurrent bleeding in cirrhotic patients [7], an observation clinically evidenced in our study.

Terlipressin should be started as soon as a variceal bleeding is suspected (ideally during transfer to hospital) and maintained afterwards for 2–5 days [8]. In our study this therapeutic scheme proved maximum efficiency.

Terlipressin has been shown to significantly improve control of bleeding and survival when compared to placebo [8] and is the only drug that has shown to improve survival. Compared with mechanical methods without the use of vasoactive drugs, using of terlipressin in association with Sengstaken-Blakemore probe tamponament, improved results. In a meta-analysis, only terlipressin has demonstrated effects on control of bleeding and on mortality [9]. Sclerotherapy in association with terlipressin improves the quality and durability of hemostasis [10]; our results attest this observation.

Conclusions

Terlipressin is an important option in obtaining hemostasis of upper gastrointestinal bleeding due to variceal rupture. Pharmacologic therapy with terlipressin can save cirrhotic patients with severe or moderate bleeding, who require transfusion of at least two units. Expanding indications of terlipressin use in other patient populations remains an issue for the future. Further research and the existence of therapeutic arsenal of terlipressin in emergency services are a necessity.

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