

THE EFFECTIVENESS AND SAFENESS OF TERLIPRESSIN THERAPY IN PATIENTS WITH UPPER GASTROINTESTINAL BLEEDING

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Abstract

Terlipressin, triglicilargininvasopressin is a vasopressin analogue used in upper gastrointestinal hemorrhages caused by ruptured esophageal varices. The present clinical trial included 43 patients and analyzed safeness and effectiveness of terlipressin treatment for upper gastrointestinal bleedings due to causes other than those specified by manufacturer's indications: portal hypertension (15 cases) and other causes of upper gastrointestinal bleeding (8 cases). A comparison was made with cases of upper digestive bleeding (20 cases) caused by ruptured esophageal varices and treated with terlipressin according to drug's indications. Matching covariates were analyzed (survival rate, blood transfusion requirements, hematocrit and the profile of side effects). The results showed a similar efficiency in both situations, and thus suggesting the extension of terlipressin's therapeutical use for causes of bleeding, other than those specified in the marketing authorization.

Rezumat

Terlipresina, triglicilargininvasopresina, este un analog de vasopresină utilizat în hemoragia digestivă superioară cauzată de ruptura varicelor esofagiene. În prezentul studiu clinic efectuat asupra 43 de pacienți s-a analizat eficiența și siguranța tratamentului cu terlipresină la bolnavi cu hemoragie digestivă superioară de cauze neincluse în indicațiile preparatului: hipertensiuni portale (15 cazuri) și alte cauze de hemoragie (8 cazuri). Compararea s-a efectuat cu sângerarea produsă de varice esofagiene care au corespuns indicațiilor terlipresinei (20 de cazuri). S-au analizat covariabilele potrivite (rata de supraviețuire, necesarul transfuzional, hematocritul, profilul de reacții adverse). Rezultatele arată o eficiență similară în cele 2 situații, sugerând extinderea aplicațiilor terapeutice ale terlipresinei pentru indicații neincluse în autorizația de punere pe piață.

Keywords: terlipressin, upper gastrointestinal bleeding, "off label" drug, observational study.

Introduction

The pharmacological modulation of vasopressin analogue as selective V1 agonist receptors has allowed the extension of their therapeutic applications. If stimulation of V2 receptors leads to reabsorption of water from renal tubules, via a cAMP dependent pathway (similar effects to the natural hormone in physiological concentrations), V1 receptors stimulation produces vasoconstriction involving inoziditic phosphatidyl transduction system coupled with Ca_{2+} ions.

Terlipressin, a vasopressin semi-synthetic analogue is characterized by unique pharmacodynamic features that clearly differentiated it from the natural hormone [1, 2, 3]:

- low antidiuretic action (only 3% of vasopressin's action) due to reduced affinity to V2 receptors;
- increased vascular muscle tone decreases splanhic vascularisation, decreases portal hypertension and compresses esophageal varices;
- increased glomerular filtration rate and sodium excretion in patients with ascites.

These features overlapp a unique pharmacokinetic profile that prints a prompt effect, a long lasting action and limited side effects as it becomes metabolic active through hydrolysis to arginine-vasopressin by successive release of glycyl rest in triglycylargininvasopressin and does not allow the accumulation of quantities that favours overdosing. As a result of these characteristics, the following indications are confirmed by terlipressin's marketing authorization: upper gastrointestinal bleeding caused by esophageal varices and emergency treatment of type I hepato-renal syndrome.

PREMISES AND AIM OF THE STUDY

Although terlipressin is authorised only in the treatment of upper gastrointestinal bleeding caused by esophageal varices and type I hepato-renal syndrome, it has proven effective in other pathologies as well: ruptured esophageal varices in patients excluded by age related criteria (over 70 years old), gastric neoplasm complicated with bleeding, severe hemorrhagic gastric or duodenal ulcers, necrotico-hemorrhagic pancreatitis. In these cases, the prescription substance is classified as medication "off label" in upper gastrointestinal bleeding from other causes than ascites or catecholamine-resistant shock. Thus, the use of terlipressin as rescue medication can save lives with a favorable benefit-risk ratio.

This paper presents our experience in treating upper gastrointestinal hemorrhage (UGH), both consecutive to liver cirrhosis and other causes, analyzing the benefit/risk ratio by quantifying the efficacy and adverse effect as well as the survival rate. The effectiveness and safety of

terlipressin were assessed comparatively in both pathologies which have official indication as well as medication "off label". Regarding long-term efficacy in patients with hepato-renal syndrome there is a controversy in the literature, a recent meta-analysis suggesting that long-term survival (over 3 months) only confirms mortality in hepato-renal syndrome, mortality not being influenced by other causes, despite the improvement of renal function [4].

Materials and Methods

The study implied a single center type group of 43 patients, including 20 with variceal UGH (age 51.2 ± 8.9 years) and 23 (aged 58.0 ± 15.1 years), with UGH from other causes, admitted to the Emergency County Hospital Targu Mures (Surgery Clinics 1 and 2, ATI Clinic no. 1 Gastro-enterology Clinics 1 and 2) in the period December 2011-January 2012. The clinical study, FE 999 908 CS 04 was approved by the Local Ethics Committee of UMF Targu Mureş (no. 11624/17.11.2010) and all patients signed informed consent. The inclusion criteria were as follows: UGH from any cause (patients with UGH consecutively to esophageal varices aged up to 70 years were separately quantified); emergency treatment with terlipressin as first therapeutic measure or associated with surgery, endoscopic treatment or other invasive maneuvers.

The parameters of monitoring the effectiveness / safety of therapy were as follows: the survival rate, the hematocrit on admission (paraclinical severity of bleeding according to the Orfanidi classification), respectively its evolution after treatment (at discharge), number of days of hospitalization and level of satisfaction of treatment according to clinical assessment of the physician, the assessment of the correlation between transfusion requirements and terlipressin dose required to control bleeding, the assessment of adverse reactions and complications of iatrogenic etiology.

Results and Discussion

On admission, assessing severity of bleeding in the two studied groups by stratification of hematocrit according to the Orfanidi classification (low severity, medium severity, high severity, severe) shows more frequent distribution at the threshold of statistical significance of more severe cases in the group of patients with non-variceal bleeding (Table I).

Table I

Orfanidi classification for the two groups

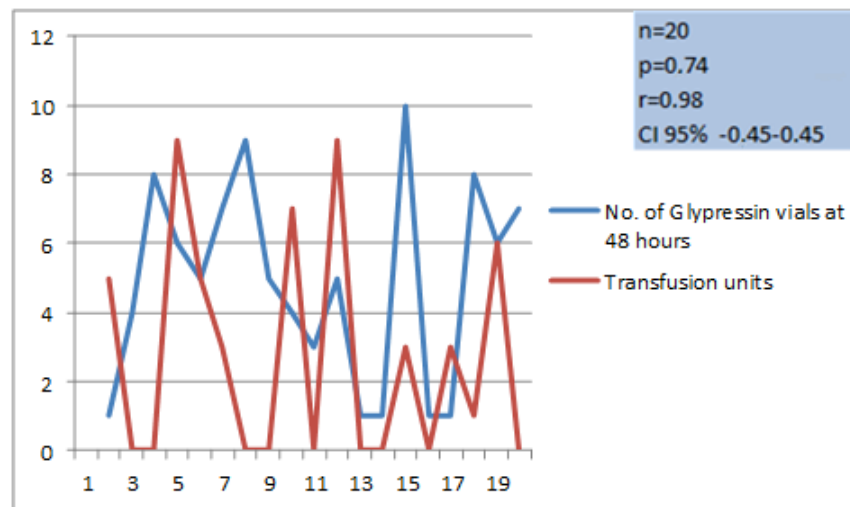
Upper digestive bleeding severity	Orfanidi classification	Cases with upper digestive bleeding – ruptured esophageal varices	%		Cases with upper digestive bleeding „off label”	%
Low	Hct >35 %	9	45.00%		4	17.39%
Medium	Hct 25-35%	6	30.00%		15	65.22%
High	Hct <25%	3	15.00%		3	13.04%
Severe	Hct <15	2	10.00%		1	4.35%
Total		20			23	
Chitest p=0.05						

Therapeutic benefit analysis

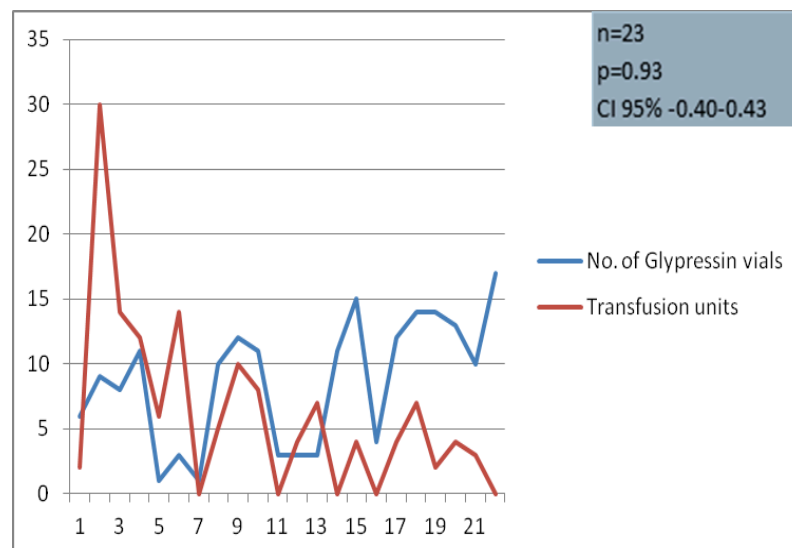
Survival after treatment in the group of patients with variceal bleeding group was 95% (1 death by hepato-renal failure from a total of 20 cases) vs. 79.31% for the other batch. Decreased survival rate in "off label" group can be explained by associated diseases (gastric cancer, acute pancreatitis, bleeding ulcer, etc.), older age (mean age 58.04 years vs. 51.2 years in variceal group, $p = 0.01$).

The study of possible relationships between effective treatment and some supposed relevant covariates (representative parameters for assessing severity, complications and patient's outcome) led to the following results:

- lack of correlation (Spermann nonparametric test) between the cumulative dose of terlipressin at 48 h after the onset of bleeding (in number of administered units - 1 mg terlipressin acetate powder vials for injection) and transfusion requirements in units transfused in both groups studied - $p = 0.74$, $r = 0.98$, CI 95% [-0.45 to 0.45] for the group with variceal bleeding, respectively $p = 0.93$, CI 95% [-0.40 to 0.43] in the group without esophageal varices - Figures 1 and 2;
- significant difference in transfusion requirements between groups, although there is no significant difference between hematocrit values (%) at admission between the 2 groups (33.30 ± 35.12 vs. 29.54 ± 6.31 , $p = 0.14$; "t" Student test); different transfusion requirements is also reflected in the improvement of hematocrit values only in the group with upper digestive bleeding "off label" to whom the combination of medication with blood transfusions was frequently required by patients' status (Table II).

**Figure 1**

Cumulative dose of terlipressin and transfusion requirement (group with variceal bleeding)

**Figure 2**

Cumulative dose of terlipressin and transfusion requirement (group without esophageal varices)

Table II

Hematocrit values (%) in the 2 studied groups

Group	Hematocrit at admission (%)	Hematocrit on discharge (%)	Transfusion units required (no)	p (t Student test) - final vs. initial
Upper digestive bleeding due to varices	33.30 ± 9.59	35.12 ± 4.07	51	0.27 (NS)
Upper digestive bleeding „off label”	29.54 ± 6.31	33.11 ± 9.59	136	0.001

NS = non significant

If the drug efficiency is expressed in terms of pharmaco-economics, by comparing the number of days of hospitalization between the 2 studied groups, there are no significant differences (9.55 vs. 11.6, $p = 0.77$, Mann-Whitney test) and the comparative subjective assessment by the physician of the clinical course of patients in the 2 groups is summarized in Table no III.

Table III

Effectiveness of medication assessed by physician based on the clinical criteria

Group UGH variceal		Group UGH „off label”	
Doctor comments	n	Doctor comments	n
Good	4	Good	2
Very good	16	Very good	16
Satisfactory	0	Satisfactory	4
Unsatisfactory	0	Unsatisfactory	1
n=20		n=23	

Assessment of adverse reactions

Treatment with terlipressin produced no serious and / or unexpected adverse effects to be imputable to medication or requiring prompt intervention. There were found only mild side effects (pallor - caused by peripheral vasoconstriction, headache, rash).

The results of a previous research [5] have confirmed the remarkable efficiency of terlipressin in patients with upper gastrointestinal bleeding caused by rupture of esophageal varices. Expanding the therapeutic applications to the other causes of upper gastrointestinal bleeding ("off label") is confirmed by this study, by analyzing the risk / benefit ratio and comparing the results with those obtained for approved indications.

In literature, results are published in which terlipressin administration was done outside of the marketing authorization. Saner FH et al. [1] emphasizes the effectiveness and safety of terlipressin in hepato-renal

syndrome and shock refractory to catecholamines (after restoration of blood volume). In the case of patients with hepato-renal syndrome unresponsive to terlipressin, a meta-analysis of Hiremath SB et al. shows that continuation of low-dose terlipressin medication (less than 4 mg / day) combined with albumin and N-acetylcysteine as an antioxidant can increase the survival rate [4].

The vasoconstrictor effect of terlipressin in reducing portal hypertension, esophageal varices compression and increased elimination of sodium in the conditions of an improvement of glomerular filtration rate in cirrhosis could add other actions to explain pharmacodynamic efficacy. Preclinical studies in an experimental model of ascites in rats, have demonstrated the efficacy of terlipressin, which has been associated with the down regulation of aquaporine AQP2 in the kidney (under the conditions in the model of ascites in rats is significantly correlated with the phenomenon of up regulation of AQP1 and AQP2 aquaporines) [6].

Terlipressin shows a small number of adverse effects and a longer half-life compared to other vasoactive agents (vasopressin, somatostatin), allowing its use *in bolus* and even in the suspicion of variceal bleeding [7]. However, the “off-label” drug use (including electronic prescribing system) is not always reimbursed by the health insurance system [8].

In our opinion [5] its use may be ideal in the primary and secondary variceal bleeding prevention, this being noticed in randomized trials [9].

In meta-analysis, only Terlipressin have demonstrated effects on control of bleeding and on mortality [10].

Association of endoscopic (ligation, variceal sclerosis) or surgical (azygo-portal disconnection) therapy improve the prognosis of hemodynamically stable patient-temporized in advance with terlipressin [7].

Conclusions

The results of the present study show that the effectiveness and safety of terlipressin in patients with upper gastrointestinal bleeding without esophageal varices is similar to that caused by the rupture of varices in cirrhotic patients, although this indication is outside the marketing authorization. Quick intervention with terlipressin (along with other endoscopic or surgical procedures) in patients with upper gastrointestinal bleeding may be salutary, patient prognostic depending on the time of intervention.

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