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VASOPRESSOR THERAPY OF HEPATORENAL SYNDROME AGAINST THE BACKGROUND OF ALCOHOLIC LIVER CIRRHOSIS

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Hepatorenal syndrome is one of the most common causes of death in liver cirrhosis, and its treatment methods are insufficiently studied, therefore, the aim of this study was to compare the effectiveness of different schemes of vasopressor therapy. A total of 109 patients with alcoholic liver cirrhosis were divided into two groups: group 1 (n=57) – received terlipressin+albumin, group 2 (n=52) – midodrine+octreotide+albumin. According to the study results, there was a significant difference in the cumulative 3–month survival in groups 1 and 2 (56.1 % vs. 28.8 %, p<0.05). In the multivariate analysis, only the complete response to treatment (risk ratio – 23.92; p<0.002) and the initial severity scores (risk ratio – 1.18; p<0.02) were predictors of 3–month survival. Terlipressin showed greater therapeutic efficacy, as it reduced mortality risk by 3.65 times (from 0.558±0.034 to 0.153±0.026) (p<0.05) and improved renal function (70.2 % in group 1 versus 28.8 % – in group 2) (p=0.01).

Key words: hepatorenal syndrome, alcoholic liver cirrhosis, terlipressin, vasopressors.

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ВАЗОПРЕСОРНА ТЕРАПІЯ ГЕПАТОРЕНАЛЬНОГО СИНДРОМУ НА ТЛІ АЛКОГОЛЬНОГО ЦИРОЗУ ПЕЧІНКИ

Гепаторенальний синдром є однією із найчастіших причин смертності при цирозі печінки, а методи його лікування є недостатньо вивченими, тому, метою даного дослідження було порівняння ефективності різних схем вазопресорної терапії. Всього було обстежено 109 хворих на алкогольний цироз печінки, які були розподілені на дві групи: група 1 (n=57) – отримували терліпресин+альбумін, група 2 (n=52) – мідодрин+октреотид+альбумін. За результатами дослідження спостерігалася суттєва різниця в кумулятивному 3–х місячному виживанні у групах 1 та 2 (56,1 % проти 28,8 %, p<0,05). При багатофакторному аналізі тільки повна відповідь на лікування (співвідношення ризиків – 23,92; p<0,002) та вихідний рівень балів за шкалою важкості (співвідношення ризиків – 1,18; p<0,02) виявилися предикторами 3–х місячного виживання. Терліпресин показав більшу лікувальну ефективність, оскільки він зменшував ризик смертності у 3,65 рази (із 0,558±0,034 до 0,153±0,026) (p<0.05) та покращував функцію нирок (70,2 % у 1–й групі проти 28,8 % – у 2–й групі) (p=0.01).

Ключові слова: гепаторенальний синдром, алкогольний цироз печінки, терліпресин, вазопресори.

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Hepatorenal syndrome (HRS) is a potentially reversible form of renal failure that occurs in patients with cirrhosis and ascites. According to the hypothesis of peripheral arterial vasodilation; HRS is caused by severe vasoconstriction of the renal arteries in response to a decrease in the effective volume of circulation [1]. However, patients with HRS have a high mortality rate while awaiting for transplantation. Moreover, the survival rates after the liver transplantation in patients with HRS are lower than in patients without it [9]. The use of splanchnic arterial vasoconstrictors leads to improved renal function in type 1 HRS, provided they are prescribed together with albumin to correct oncotic blood plasma pressure [10–14]. Terlipressin, a derivative of vasopressin, is the most common vasoconstrictor in Europe due to its effectiveness and convenience [3] and it has the ability to improve renal function in 40 %–50 % of patients [5, 13]. In countries such as the United States, where terlipressin is not used, uncontrolled studies of HRS have been performed with the midodrine+octreotide+albumin regimen [11], which yielded about 40 % efficacy. The high cost of terlipressin therapy encourages the search for alternative vasopressor drugs, one of which is octreotide and midodrine.

However, to date there are very few studies comparing the effectiveness of different schemes of vasopressor therapy of HRS.

The purpose of this study was to compare the effectiveness of terlipressin+albumin and midodrine+octreotide+albumin for the treatment of hepatorenal syndrome in patients with alcoholic liver cirrhosis.

Material and methods. The study enrolled a total of 109 patients with alcoholic liver cirrhosis (ALC), who were hospitalized to the CSI "Chernivtsi Regional Narcological Dispensary" in Chernivtsi in the period from January 2011 to December 2018. HRS was diagnosed according to the clinical guidelines of the European Association for the Study of the Liver – EASL (2018) [5].

The severity of patients was assessed by MELD score (Model for End Stage Liver Disease) in points: MELD=9.6*ln (creatinine (Cr), mg/dl)+3.8*ln (bilirubin, mg/dl)+11.2*ln (international normalized ratio, INR)+6.4 [11].

Systolic blood pressure was measured by N.S. Korotkoff method using the manual tonometer "Microlife BP AG 1–20", Switzerland. Mean blood pressure (MBP) was calculated by Hickem's formula: divide the value of pulse pressure by three and add the value of minimum or lower blood pressure.

All patients were divided into 2 groups depending on the type of treatment prescribed: group 1 (n=57) – received terlipressin+albumin, group 2 (n=52) – midodrine+octreotide+albumin.

In all patients included in the study, albumin (Albumin–Biopharma 20 %; LLC "Biopharma Plasma" Ukraine) was administered intravenously (iv), 1 g/kg per day on the first day of treatment and 20–40 g/day – in the following days.

In group 1, terlipressin (Remestip, Ferring–Lechiva AS, Czech Republic) was initially administered at a dose of 3 mg/24 hours by continuous intravenous administration. Response to treatment was assessed every 48 hours. If Cr decreased by less than 25 % from the baseline, the dose was gradually increased to 12 mg/24 hours.

In group 2, midodrine (Gutron, Nicomed, Austria) was administered per os at an initial dose of 7.5 mg every 8 hours, octreotide (Octreotide–MB, Bendalis GmbH, Germany) was administered intravenously at an initial dose of 100 mg every 8 hours. In all groups, treatment was continued until the Cr decreased to 133 mmol/l (or for a maximum of 14 days) and continued for another 24 hours after response to treatment. The complete response was considered to be a decrease in Cr to ≤133 mmol/l (responders), a partial response was considered to be a decrease in Cr by 50–60 % of the initial level (partial responders), and a partial response was considered to be a decrease of Cr by less than 50 % (nonresponders).

The exclusion criteria were: chronic kidney disease (baseline Cr 4.0 mg/dl), non–alcoholic etiology of cirrhosis, delirium, surgery, portal vein thrombosis, obstructive jaundice, decompensation of comorbidities.

The studies were performed in accordance with the basic bioethical requirements of the Fundamental Guidelines for Clinical Research ICH GCP 1996, as well as the Declaration of Helsinki (Declaration of Helsinki 2004), the Common European Directive (EU Directive 2001/20/EC). of the European Directive 2005/28/EC.

Statistical analysis. The primary endpoint of the study was considered to be the complete response to treatment, and it was used to calculate the sample size. Group comparisons were performed using Student's t–test or Wilcoxon's rank summary test for the continuous data, and the χ–square or Fisher's exact test for the categorical data. Patient survival was assessed by the Kaplan–Meier method and compared in groups using a logarithmic test. Variables that were predictors of response to treatment and survival with a value of $p<0.5$ in one–dimensional analysis were included in the multivariate logistic regression model; where the results were presented as odds with a 95 % confidence interval. All tests were two–tailed. $p<0.05$ was considered statistically significant with an error of α 5 % and β error of 20 %. Statistical analysis of the data was performed using the software RStudio1.1.463.

Results of the study and their discussion. The clinical and laboratory data at the study onset did not differ significantly in both groups. Patients' average age, when enrolled in the study, was (42.34±12.57) years; the history of ALC – (3.5 ± 1.54) years; the history of alcohol abuse (8.42±3.53) years; the gender distribution was 79.6 % (n=119) men and 20.4 % (n=31) women ($p<0.05$). The incidence of different types of HRS (type 1 or type 2) was also approximately the same – so, HRS type 1 was 92.9 % in the group 1 and 90.4 % – in the group 2. The average age of the subjects in group 1 was 45±7.5 years, the ratio of male to female – 85.3 %: 14.7 %, MBP – 76.8±8.1 mm Hg, MELD score – 31.2±65.8. The average age of the subjects in group 2 was 43±6.8 years, the ratio of male to female – 84.7 %: 15.3 %, MBP – 76.5±8.3 mm Hg, MELD score – 31.3±65.6.

Improvement in renal function was significantly more common in the group 1: 40 of 57 patients in group 1 (70.2 %) had a complete or partial response compared to 15 of 52 (28.8 %) in the group 2 ($p=0.01$); 31 of 57 patients in the group 1 (55.4 %) had a complete response, compared with 3 of 52 in the group 2 (5.8 %) ($p<0.001$). The decrease in Cr level in patients with complete response was more noticeable in the group 1 (from 323.2±91.1 mmol/l to 121.6±30.0 mmol/l) than in the group 2 (from 332, 8±85.1 mmol/l to

159.8±15.9 mmol/l), but the difference was not statistically significant. The decrease in Cr in the total population of patients of the group 1 (from 326.8±88.4 mmol/l to 221.1±162.8 mmol/l) was more statistically significant than in the group 2 (from 343.9±187.5 mmol/l – up to 326.4±273.2 mmol/l; p<0.035). In the group 1, 29 of the 31 complete responders responded to 3 mg/day of terlipressin and 12 responded to 6 mg/day of terlipressin. As for the 9 partial responders, they all received the maximum allowable dose of 3 mg/day in the first three patients, 6 mg/day in the next 4 patients and 12 mg/day in the other two patients. In 3 complete responders in group 2, improvement occurred after a dose of midodrine 22.5 mg/day, with the addition of octreotide – 300 mg/day. Twelve partial responders in group 2 received a maximum dose of 37.5 mg/day of midodrine plus 600 mg/day of octreotide in 8 patients and 22.5 mg/day of midodrine plus 300 mg/day of octreotide in the remaining 4 patients. There were no significant differences between the two groups in terms of treatment duration (8.2±4.4 days in the group 1 versus 9.1±5.0 days in the group 2; p>0.05) and in the total dose of albumin after the initial load (264.8±200.2 g versus 313.6±185.4 g; p>0.05). MBP was significantly higher in the group 1 versus group 2 after 3 days of treatment, as well as in the middle of the treatment period.

There were no significant differences between the two groups in terms of the number of patients who survived 1 and 3 months: 40/57 (70.2 %) and 33/57 (57.9 %), respectively, in the group 1; and 35/52 (67.3 %) and 22/52 (42.3 %), respectively, in the group 2 (p>0.05). Responders (complete and partial) showed a 3–fold better survival than non–responders (p<0.001). The distribution of values of survival time in the studied patients was as follows (fig. 1).

The estimated probability of survival for each of the group members was found using Kaplan Meyer's procedure (fig. 2).

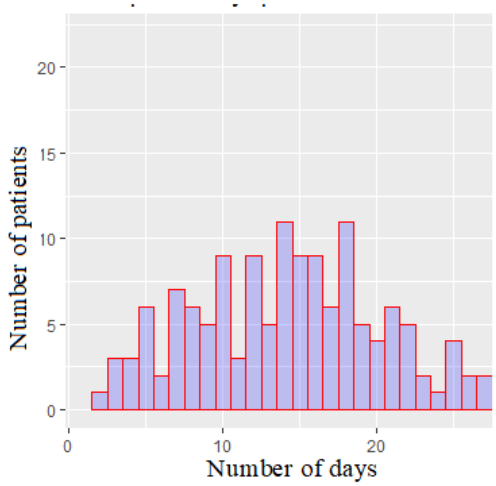

Fig. 1. The average survival rate of patients with HRS on the background of ALC

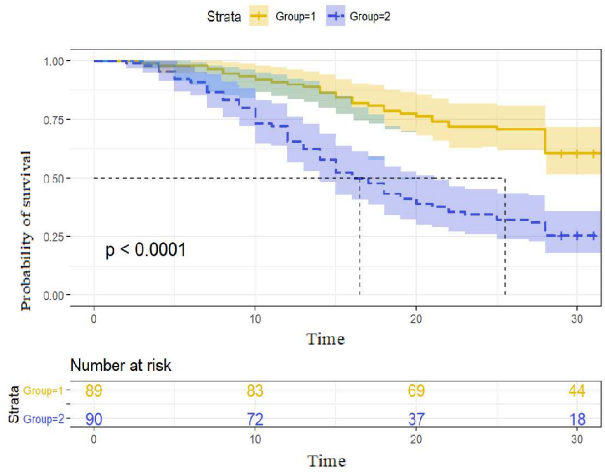

Fig. 2. Graph of survival function of patients with HRS on the background of ALC, depending on the type of treatment received

Next, we detected the magnitudes of risks for each of the groups, which were characterized by the risk function. The risk function λ was defined as the velocity of the event at time t provided to survive before time t or later (i.e., *Tt*):

$$\lambda(t) = \lim_{dt \to 0} \frac{\Pr(t \le T < t + dt)}{dt \cdot S(t)} = \frac{f(t)}{S(t)} = -\frac{S'(t)}{S(t)}.$$

Here $f(t) = F'(t) = (1 - S(t))'$ is a function of the density of the distribution of life time.

That is, the average risk of death was 0.53±0.026 for the group 1, and 0.558±0.034 – for group 2. The risk in group 2 increased by 3.65 times compared to group 1 (fig. 3).

The difference in cumulative survival between all responders (partial and complete) and non–responders was statistically significant in the group 1 (p<0.001), but not in the group 2 (p>0.05), probably due to more frequent appointment of the rescue treatment. Also in the group 1, better 3–month survival was found in patients who did not receive the rescue treatment than in the group 2 (56.1 % vs. 28.8 %, p<0.05). Finally, among all randomized patients in general, there was a significant difference in cumulative 3–month survival between responders and non–responders (73.7 % versus 38.4 %, respectively; p<0.025).

In the multivariate analysis (taking into account the initial level of Cr, MBP, complete response to treatment and baseline MELD score) only a complete response to treatment (risk ratio – 23.92; 95 % CI – 3.21–156.75; p<0.002) and the initial level of scores on the MELD scale (risk ratio – 1.18; 95 % CI – 1.4–1.42; p<0.02) were the predictors of 3–month survival.

Renal vasoconstriction is mediated by renin–angiotensin and sympathetic nervous systems and non–osmotic secretion of vasopressin. he decrease in effective circulating volume is a consequence of severe splanchnic vasodilation and low cardiac output. Bacterial infections provoke HRS due to the inflammatory vasodilation and increased cardiovascular dysfunction in liver cirrhosis. There are two types of HRS. Type 1 HRS is characterized by sudden and rapidly progressive renal failure, manifested by doubling the initial serum Cr to more than 226 mmol/l (2.5 mg/dL) in less than 2 weeks. Type 2 HRS is characterized by the moderate renal failure (serum Cr 133–226 mmol/l or 1.5–2.5 mg/dl), with a constant or slowly progressive course. The average life expectancy in untreated patients with HRS is about 2 weeks, so liver transplantation is the treatment of choice [9].

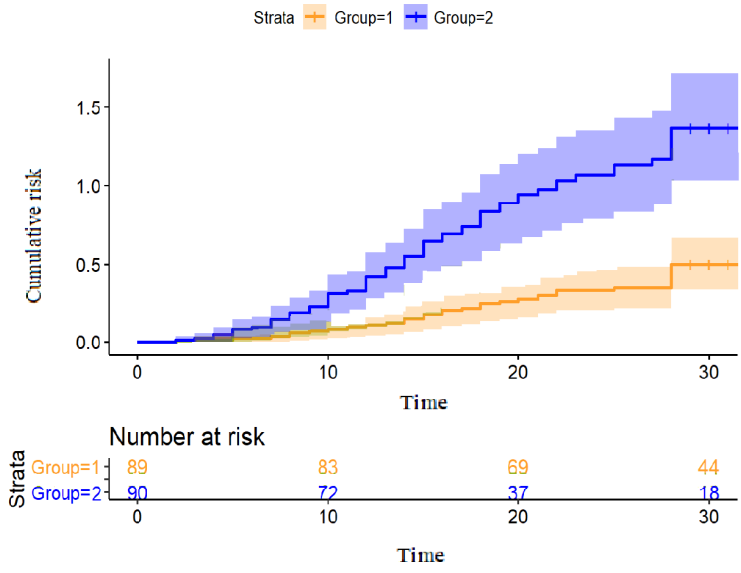

Fig. 3. Graph of the cumulative risk curves in patients with HRS on the background of ALC, depending on the type of treatment received

As a result of our study, we found a significant advantage of terlipressin+albumin scheme for improving the renal function in HRS patients, compared with midodrine+octreotide+albumin scheme, which can be explained by the better ability of terlipressin to increase MBP ($p<0.05$). The response rate to midodrine treatment (28.6 %) was generally consistent with the literature, however, was lower than in previous retrospective studies by Mattos ÂZ et al. (40 %) [8], but higher than in Sanyal et al. (18 %) [3]. This discrepancy can be explained by the fact that in the above studies, the restoration of the volume of circulating plasma in HRS type 1 was performed using saline; more than 50 % of the patients involved had viral cirrhosis, in which recovery of renal function could occur only as a result of improvement in the underlying liver disease; terlipressin bolus was administered intravenously every 4 or 6 hours. This regimen may reduce the vasoconstrictor effect of terlipressin, as recent pharmacodynamic studies have shown that the maximum effect of terlipressin lasts less than 4 hours [7]. Therefore, in our study, terlipressin was administered intravenously continuously. Second, according to the International Ascites Club's 2007 diagnostic criteria, patients with renal failure and active bacterial infections are considered to have HRS. Recent observations suggest that the response rate to terlipressin+albumin in patients with HRS caused by infection is only 67 % [8]. For ethical reasons, non–responders were provided with the rescue treatment, including the possibility of transition from one treatment regimen to another. Thus, it should be noted that the study design was not perfect for evaluating the effectiveness of randomized treatment for 1–month and 3–month survival as a secondary endpoint.

Thus, the analysis of the results of the study allowed us to draw some conclusions about survival. First, the response to treatment was an independent predictor of survival. Second, the difference in 1–month and 3–month survival between respondents and non–responders was greater in the group 1 than in the group 2. In explaining this fact, the large impact of rescue treatment on renal function and/or survival in non–responders in the group 2 should be taken into account. Thus, 3–month survival was higher in the group 1 than in the group 2, provided that patients did not receive rescue treatment. It should also be noted that the frequency of serious side effects and/or adverse events that would lead to the discontinuation of treatment did not differ significantly in both groups, despite the greater vasoconstrictor effect of terlipressin. However, stroke and hypertension were observed only in patients treated with terlipressin. As for circulatory overload and arrhythmia, they may also be related to factors other than the vasoconstrictor effect, such as renal failure and/or electrolyte imbalance.

Conclusions

The results of the study indicate that vasopressor therapy with terlipressin+albumin is more effective for the treatment of patients with hepatorenal syndrome, developed on the background of

alcoholic liver cirrhosis, compared with midodrine and octreotide+albumin, because it reduces the risk of death in 3.65 times (from 0.558±0.034 to 0.153±0.026) ($p<0.05$) and improves the renal function (70.2 % of patients in group 1 had a complete or partial response to treatment, compared with 28.8 % in group 2) ($p=0.01$). Thus, terlipressin in combination with albumin can be considered the therapy of choice for the treatment of this pathology.

Prospects for further investigations. Given the high cost of terlipressin, it would be appropriate to conduct a pharmacoeconomic analysis of various schemes of vasopressor therapy of HRS in patients with ALC.

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