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The Role of Correcting Structural and Functional Albumin Properties in Ascites Control in Decompensated Cirrhotic Patients

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Aim: to study the structural and functional characteristics of albumin in patients with decompensated cirrhosis, their relationship with ascites; to identify the relationship between improvement in albumin characteristics and regression of ascites.
Materials and methods. Fifty patients with decompensated liver cirrhosis and ascites were divided into groups. The first group received standard treatment for cirrhosis, the second — standard treatment and replacement therapy with 20 % human albumin solution at a dose of 200 mL per week for 3 months.
Results. The value of the native conformation of albumin and the functional parameters of albumin were significantly lower than in the group of healthy individuals ($p < 0.001$). With the severity of ascites, the native conformation index (DR), which characterizes the structural usefulness of the albumin molecule, decreased. Median DR for ascites stage I (IAC) was –1.69, II grade — –2.28, III grade — –2.42 ($p < 0.05$). Replacement therapy with albumin allowed to achieve regression of ascites in 48.4 % of patients, compared with 7.1 % in the standard treatment group. Along with clinical improvement, restoration of albumin structural and functional properties was observed in the albumin group. The mean serum albumin level at which ascites remained in remission for 3 months was 42.11 g/L ($p < 0.001$).
Conclusions and discussion. The structural and functional characteristics of albumin were impaired in patients with decompensated cirrhosis and ascites. The severity of changes in the structural and functional properties of albumin depended on the severity of ascites. The regression of ascites was accompanied by the restoration of the functional and structural usefulness of albumin against the backdrop of albumin replacement therapy. The criterion for stopping transfusion therapy with albumin can be the achievement of a serum albumin level of 42.11 ± 7.04 g/L, DR — 1.05, BE — 73.51 %, RTQ — 75.10 %, DTE — 72.71 %.
Keywords: DR, BE, RTQ, DTE, EPR, albumin transfusions, albumin replacement therapy, ascites
Conflict of interest: the authors declare no conflict of interest.

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Роль коррекции структурно-функциональных показателей альбумина в контроле асцита у пациентов с декомпенсированным циррозом печени

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Цель исследования: изучить структурно-функциональные характеристики альбумина у пациентов с декомпенсированным циррозом печени, их связь с асцитом, выявить связь улучшения характеристик альбумина и регрессии асцита.
Материалы и методы. Пятьдесят пациентов с декомпенсированным циррозом печени и асцитом разделили на группы. Первая группа получала стандартное лечение цирроза, вторая — стандартное лечение и заместительную терапию 20 %-ным раствором альбумина человека в дозе 200 мл в неделю на протяжении 3 месяцев.
Результаты. Величина нативной конформации альбумина и функциональные показатели альбумина были значимо и достоверно ниже, чем в группе здоровых лиц ($p < 0,001$). По мере выраженности асцита показатель нативной конформации (DR), характеризующий структурную полноценность молекулы альбумина, снижался. Медиана DR при асците I ст. (IAC) составила –1,69, при асците II ст. — –2,28, при III ст. — –2,42 ($p < 0,05$). Заместительная терапия альбумином позволила добиться регрессии асцита у 48,4 % больных по сравнению с 7,1 % в группе стандартного лечения. Наряду с клиническим улучшением наблюдалось восстановление структуры и функций альбумина в группе лечения альбумином. Средний уровень

альбумина сыворотки крови, при котором сохранялась ремиссия асцита в течение 3 месяцев, составил 42,11 г/л ($p < 0,001$).
Выводы и обсуждения. Структурно-функциональные характеристики альбумина были нарушены у пациентов с декомпенсированным циррозом и асцитом. Степень выраженности изменений структурно-функциональных свойств альбумина зависела от тяжести асцита. Регрессия асцита сопровождалась восстановлением функциональной и структурной полноценности альбумина на фоне заместительной терапии альбумином. Критерием прекращения трансфузионной терапии альбумином может служить достижение уровня альбумина в сыворотке крови 42,11 ± 7,04 г/л, показателя DR — 1,05, BE — 73,51 %, RTQ — 75,10 %, DTE — 72,71 %.
Ключевые слова: DR, BE, RTQ, DTE, ЭПР, трансфузии альбумина, заместительная терапия альбумином, асцит
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Introduction

Ascites is one of the most common complications of liver cirrhosis (LC), along with hepatic encephalopathy and bleeding from varicose veins of the esophagus and stomach [1]. Often the first manifestation of decompensation in cirrhotic patients is the onset of ascites. Patients with Child — Pugh A cirrhosis progress towards decompensated cirrhosis at a rate of 5–7 % annually. Ten years after the diagnosis of hepatic cirrhosis, 50 % of patients develop ascites. The survival rate of patients at the decompensated cirrhosis stage with ascites over one and two years is 60 and 45 %, respectively. While patients with compensated cirrhosis live much longer: 95 % of patients survive for one year and 90 % for two years [2–4].

Over the past few years, new approaches to the cirrhosis treatment have been widely studied, which can stabilize the course of the disease and provide reliable control over ascites. One promising area is long-term albumin replacement therapy. Moreover, until recently, indications for short-term albumin transfusions were acute kidney injury, spontaneous bacterial peritonitis, and large volume paracentesis [1]. At the same time, the use of albumin replacement therapy in a long time period also finds its place in clinical practice [5].

In a study performed by Italian scientists — ANSWER, it was shown that prolonged therapy with albumin at a dose of 40 g per week for 24 months improved the life quality of patients, contributed to better control of ascites, and increased life expectancy [6]. This treatment regimen is included in the European and Russian clinical guidelines [7, 8]. However, the high cost of such prolonged treatment creates prerequisites for further research and optimization of the albumin replacement therapy regimen.

In liver cirrhosis, not only does the amount of serum albumin decrease, due to the inhibition of the protein-synthetic function of the liver, but its structural and functional properties also change, which affect its ability to fully perform its functions [9, 10]. These data can be used to optimize the duration of albumin replacement therapy. However, to date, it has not been studied whether albumin replacement therapy leads to the restoration or improvement of the characteristics of serum albumin, and whether it is possible to rely on these data in choosing a therapeutic strategy.

The aim of our work was to study the structural and functional characteristics of albumin in patients with decompensated cirrhosis and their relationship with ascites, and to identify a possible relationship between improvement in albumin characteristics and ascites regression.

Materials and methods

To solve this problem, patients with decompensated cirrhosis complicated by ascites ($n = 50$) were divided into two groups. The first group received standard medical therapy ("SMT"), depending on the disease etiology. The second group received standard therapy and additional replacement therapy with a 20 % human albumin solution at a dose of 200 mL per week for 3 months ("SMT + Albumin"). The third, control, group included 12 healthy participants to compare the indicators of the structure and functions of albumin.

The study was approved by the local ethics committee (No. 31–20 of 11.11.2020). Upon admission to the hospital, patients underwent a standard examination as part of the clinical guidelines for managing patients with cirrhosis. Examinations similar to the baseline were performed in all patients after 3 months of treatment. To assess the structural and functional state of serum albumin, spectroscopy was performed by the method of electron paramagnetic resonance (EPR). The measurements were performed on an ESR-Analysator MMS 01–08 analyzer (MedInnovation GmbH, Germany). A set of reagents for *in vitro* determination of the functionality of albumin in blood serum using the MMS-kit-SA01 spin probe (MedInnovation GmbH, Germany). EPR spectroscopy makes it possible to evaluate the structure of a protein molecule and detect changes in

the conformation of the molecule that occur under various conditions [11].

Structural and functional characteristics of albumin were evaluated according to the following reference values: native conformation (DR) was considered normal at a value above 1.2, binding efficiency (BE) — above 65 %, transport activity (RTQ) — above 60 %, and detoxification capacity (DTE) — above 50 %.

Statistical analysis was carried out using the StatTech v. 2.8.8 (Stattech LLC, Russia).

Results

Characteristics of patients included in the study

During the interpretation of the obtained data, the groups were comparable in terms of demographic characteristics ($p > 0.05$). Alcoholic cirrhosis was the leading cause of liver disease in 31 (62.0 %) cases, in 5 (10 %) cases it was viral hepatitis.

The "SMT + Albumin" group included 18 patients with class B cirrhosis (51.4 %) and 17 patients with class C (48.6 %). The "SMT" group included 7 (46.7 %) and 8 (53.3 %) patients, respectively. There were no significant differences between the groups ($p > 0.05$; Fisher's exact test). There were also no statistically significant differences in the initial data of the main clinical and instrumental parameters of patients between the treatment groups ($p > 0.05$).

In the "SMT + Albumin" group, ascites stage I according to the IAC classification was observed in 12 patients (34.3 %), stage II — in 16 (45.7 %), and stage III — in 7 (20.0 %). In the "SMT" group: stage I — in 6 patients (40.0 %), stage II — in 5 (33.3 %), and stage III — in 4 (26.7 %). There were no significant baseline differences between the treatment groups ($p > 0.05$; Pearson's Chi-square).

Interpretation of the data obtained showed that the initial structural and functional parameters of albumin in the formed groups were comparable ($p > 0.05$). In the "SMT + Albumin" group, the median DR was –2.08, BE — 35.44 %, RTQ — 36.36 %, and DTE — 24.98 %. In the "SMT" group, the median DR was –2.13, BE — 34.12 %, RTQ — 36.07 %, and DTE — 24.71 %.

Baseline values of total serum albumin concentration in the groups of patients also did not differ: the mean value of albumin was 31.84 ± 6.11 g/L in the "SMT + Aalbumin" group and 30.58 ± 7.61 g/L in the "SMT" group ($p > 0.05$; *t*-Student's criterion).

When comparing albumin with a group of healthy volunteers, a significant and reliable decline in all structural and functional parameters was noted. Thus, the average value of the DR index in patients corresponded to a negative value of –2.09, in the group of healthy individuals — 3.51; BE in the group of patients was significantly lower than in healthy individuals — 37.26 ± 16.55 % vs. 111.67 ± 21.73 %; RTQ — 38.40 ± 16.41 % vs. 79.98 ± 12.37 %; DTE — 24.84 % vs. 98.19 % ($p < 0.001$). Thus, the study proved a significant and reliable decrease in the structural and functional activity of albumin in patients with decompensated liver cirrhosis compared to a group of healthy individuals.

As the ascites became more pronounced, the indicator of native conformation — DR, which characterizes the structural nativity of the albumin molecule, decreased. Median DR for ascites stage I (IAC) was –1.69, stage II — –2.28, stage III — –2.42 ($p < 0.05$; Kruskal — Wallis test). BE, RTQ, and DTE had no significant difference ($p > 0.05$). Thus, the work showed the relationship between violations of the functional usefulness of albumin and the severity of ascites. In particular, the DR index, which reflects the severity of albumin conformational albumin violations, decreased as ascites progressed.

The evaluation of treatment results after 3 months

Three patients withdrew from the study during the follow-up period. In the "SMT + Albumin" group, one liver transplant was performed and one case was fatal. There was one death in the "SMT" group. Forty-seven patients were available for further analysis. On the background of albumin replacement therapy in the "SMT + Albumin" group, the proportion of patients who improved from the decompensation stage to the compensated phase was 39.4 % ($n = 13$). At the same time, no compensation phenomena were observed in the "SMT" group (0 %; $p < 0.001$).

The average level of albumin in the "SMT + Albumin" group also increased significantly from 31.75 to 40.06 g/L ($p < 0.001$; paired Student t-test). A decrease in ESR was noted in both groups: in the "SMT + Albumin" group — from 32 to 19 mm/h ($p = 0.001$; Wilcoxon test), in the "SMT" group — from 32 to 28 mm/h ($p = 0.019$; Wilcoxon test). During the analysis of CRP in the "SMT + Albumin" group, there was a significant decrease — from 7 to 2.24 mg/L ($p < 0.001$; Wilcoxon test). Differences between groups in this indicator during treatment reached a statistically significant threshold ($p = 0.005$; Mann — Whitney *U*-test).

The analysis showed that in the "SMT + Albumin" group, complete regression of ascites was achieved in 48.4 % of cases ($p < 0.001$; Wilcoxon test), while in the "SMT" group, ascites was not detected only in 7.1 % of patients. Differences between groups during treatment were statistically significant ($p = 0.042$; Pearson's Chi-square) (Fig.).

Thus, the work showed that the use of albumin substitution therapy with over three months of treatment resulted in a 48.4 % regression of the ascites, compared to 7 % in the "SMT" group. At the same time, there was an increase in the parameters of the structure and functions of serum albumin during transfusion therapy. Among patients with decompensated cirrhosis receiving albumin replacement

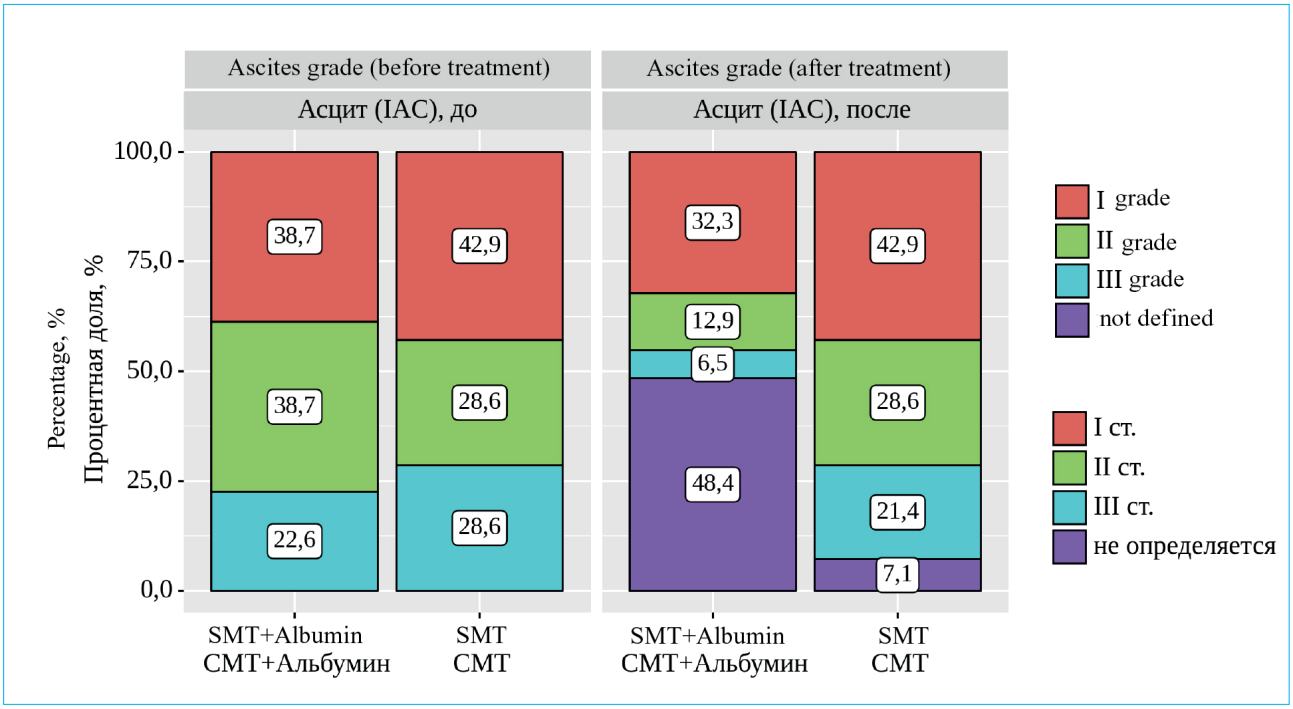

Figure. Initial severity of ascites before and after treatment in "SMT + Albumin" and "SMT" groups

Рисунок. Исходные показатели тяжести асцита до и после лечения в группах «СМТ + Альбумин» и «СМТ»

therapy, the proportion of patients with normal albumin structure increased from 0 to 42.4 % ($p < 0.05$). In the "SMT" group, the DR index retained its pathological phenotype in 100 % of patients. The binding capacity of albumin increased from 9.1 to 60.6 % ($p < 0.05$). In the "SMT" group, the BE index did not change significantly. The percentage of patients recovering normal albumin transport function increased from 18.2 to 63.6 % ($p < 0.05$); in the "SMT" group, it slightly decreased from 21.4 to 14.3 % ($p < 0.05$). The proportion of patients who achieved normal DTE values increased from 27.3 to 60.6 % (p < 0.05). While in the "SMT" group, this indicator practically did not change: 21.4 % vs. 28.6 % ($p > 0.05$).

Thus, after the use of albumin substitution therapy for three months, not only increase in the level of serum albumin has been observed, but also a recovery of its structure and functional activity.

To assess the effect of albumin levels and its structural and functional properties on the presence of ascitic syndrome during treatment, patients were divided into two groups — without ascites and with ascites of any severity. This made it possible to establish that the average value of serum albumin in the group of patients who achieved regression of ascites was 42.11 g/L, while with ascites albumin level remained at 33.96 g/l ($p < 0.001$).

The absence of ascites was accompanied by a higher native albumin conformation of 1.05. In patients who did not achieve remission of ascites this parameter made –1.90 ($p < 0.001$). The binding capacity was also higher in patients without ascites (73.51 %) compared with the group of patients with ascites (39.57 %; $p < 0.003$). Indicators of transport activity (75.10 %) and detoxification ability (72.71 %) significantly exceeded those of patients with ascites — 40.23 % and 29.83 % ($p < 0.001$ and $p = 0.014$), respectively.

Additionally, we found that among patients who achieved complete regression of ascites after 3 months of treatment, the serum albumin level was 42.11 ± 7.04, DR — 1.05, BE — 73.51 %, RTQ — 75.10 %, DTE — 72.71 %. The data obtained can serve as a guideline for stopping albumin transfusions.

Conclusions and discussion

The study revealed a significant deviation from the normal parameters of the structure and functional activity of albumin in patients with decompensated cirrhosis and ascites. Alteration of the structural and functional properties of albumin is observed in ascites, and the regression of ascites is accompanied by the restoration of the functional and structural usefulness of albumin during the albumin replacement therapy. Since conformational changes of the molecule (DR) progressed as the severity of ascites worsened, the data obtained may indicate a possible relationship between the development of ascites in patients with cirrhosis and structural albumin impairment.

Additionally, the work showed that among patients who achieved complete regression of ascites after 3 months of transfusion therapy, the serum albumin level was 42.11 ± 7.04, DR — 1.05, BE — 73.51 %, RTQ — 75,10 %, DTE — 72.71 %. The data obtained can serve as a guideline for stopping albumin transfusions. At the same time, our work is unique; there are no similar studies in world literature. Perhaps further development of this field will provide more detailed information and serve as a prerequisite for the creation of a personalized scheme of albumin substitution therapy.

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