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EFFICACY OF ALBUMIN DIALYSIS AS A BRIDGE TO TRANSPLANTATION IN CHILDREN WITH END-STAGE LIVER DISEASE

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Liver transplantation is the only effective treatment modality for end-stage liver disease. However, donor organs are not always available. In some cases, the gravity of the patient's condition makes transplantation impossible. In this regard, the use of artificial liver support systems helps in preparing a patient for transplant surgery. **Objective:** to conduct a retrospective study aimed at evaluating the efficiency of fractionated plasma separation and adsorption system. **Materials and methods.** From January 2019 to May 2020, 139 pediatric liver transplants were. We analyzed the data of 5 pediatric patients (2 girls and 3 boys, aged 12 to 17 years) who received fractionated plasma separation and adsorption (FPSA) sessions as a bridge to transplantation. The main clinical indication for FPSA was severe hepatic encephalopathy (grade 3 according to the West Haven Criteria), which was observed at 350–872 μmol/L (average 597 ± 98 μmol/L) serum bilirubin level. The FPSA sessions were conducted on a Prometheus device using AV-600 hemofilters as dialyzers (*Fresenius Medical Care, Germany).* **Results.** Depending on the extent of bilirubinemia in patients, it took from one (in one case) to three (in one case) daily FPSA sessions to restore clear consciousness, appetite and physical activity. Average bilirubin levels after treatment cycles decreased from 597 ± 98 to 236 ± 73 μmol/L. All patients successfully underwent liver transplant surgery within two to five days, two patients received a liver fragment from a living related donor. **Conclusion.** The FPSA system stabilizes the condition of potential recipients with acute liver failure. Further research is required to develop optimal regimens for albumin dialysis.

Keywords: cirrhosis, liver failure, albumin dialysis, liver transplantation, pediatric liver transplantation, extracorporeal liver support, hepatic encephalopathy, fractionated plasma separation and adsorption.

INTRODUCTION

Transplantation is the only radical method of treating patients with terminal liver diseases. However, the donor organ is not always available at the right time, and in some cases successful transplantation is hindered by the severity of the patient's condition. In such cases, the use of artificial liver support systems allows the patient to get prepared for transplantation. Over the last decades, a large number of such systems have been developed, both biological systems with hepatocytes and fully artificial [1–3]. Of the latter, systems based on albumin dialysis with membranes of high, up to 250 kDA, cutoff point, and containing a standard hemodialysis block for the injection of water-soluble substances [4]. Most of the studies of the past two decades focus on the use of albumin dialysis in cases of acute or acute chronic liver failure, are highly heterogeneous in the patients included, and therefore have hardly comparable results.

The purpose of the present retrospective study was to assess the efficacy and safety of one of the albumin dialysis systems, fractionated plasma separation and adsorption (FPSA) in the practice of the transplant center in the preparation of pediatric and adolescent patients with terminal hepatic failure for urgent liver transplantation.

MATERIALS AND METHODS

Patients

From January 2019 to May 2020, 139 transplants were performed in the pediatric patients (under 18 years of age). During this period, 5 children received at least one FPSA session in the preoperative period. Severe hepatic encephalopathy was the main clinical indication for the use of FPSA, assessed on the West-Haven Criteria [5]. The study was performed in compliance with the ethical principles of biomedical research as reflected in the World Medical Association Declaration of Helsinki. All medical interventions are envisaged by the standard protocols of the Center.

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Fractionated plasma separation and adsorption sessions

The FPSA sessions were done on the Prometheus device (a schematic diagram of the extracorporeal circulation see Fig. 1). AV 600–1000 hemofilters (*Fresenius Medical Care, Germany*) were used as hemodialyzers. The standard session lasted for 6 hours at a blood flow rate of 180–250 ml/min and a circulation rate in the albumin circuit of 300–350 ml/min.

Vascular access was performed with standard 12F dual-lumen dialysis catheters implanted into the right IJV under ultrasound control. At this, coagulopathy and thrombocytopenia did not contraindicate vascular access.

The number of FPSA sessions was determined by the availability of a cadaver or live related donor for liver transplantation. Albumin dialysis sessions were carried out in the ICU every day until clear clinical improvements manifested by the elimination of manifestations of hepatic encephalopathy in the form of restored consciousness, physical activity and appetite.

A bicarbonate acetate-free dialyzing liquid of the following composition was used: Na^+ – 138–140, K^+ – 4.0; Ca^{++} – 1.75; Mg^{++} – 1.0; glucose – 10.0; bicarbonate – 32.0 (mmol/l) with a flow of 500 ml/min at 36.0–36.5 °C. Ultrafiltration was performed in volumes corresponding to transfusion therapy during the procedure. Anticoagulation in the extracorporeal circuit was carried out by dosed administration of heparin along two lines, before the plasma filter and along the additional line, before the hemodialyzer under the control of ABC and APTT.

Surgical techniques, immunosuppression protocols, and the principles of examination of related donors are detailed in previous publications [6–9].

Statistical analysis

Demographic and clinical data are expressed as frequency and percentage for qualitative variables and as mean and standard deviation (SD) for quantitative variables. To compare parametric indicators between groups, the Student's t-test was used and for comparison of non-parametric indicators Fisher's exact test. When testing statistical hypotheses, differences were considered statistically significant at $p < 0.05$. All calculations and data analysis were performed with SPSS version 23 software package (IBM, USA).

RESULTS

The clinical and demographic characteristics of patients are given in Table 1. Attention is drawn to the adolescence of patients in the study group (12.4 years, SD ± 3.4; $p = 0.004$), as well as diseases that led to terminal liver disease: Wilson disease (one case), autoimmune hepatitis (one case); in three cases the etiology of terminal liver damage has not been verified. The mean PELD/MELD level was higher than in the general group (34.2, SD ± 9.6; $p = 0.017$), and the UNOS status corresponded to 2a or 1. Of the five patients receiving FPSA, two patients were hospitalized directly in the ICU, three were transferred for treatment within two to three days after admission. The main clinical indication for FPSA was severe hepatic encephalopathy (grade 3 according to the West Haven Criteria). Similar symptoms were

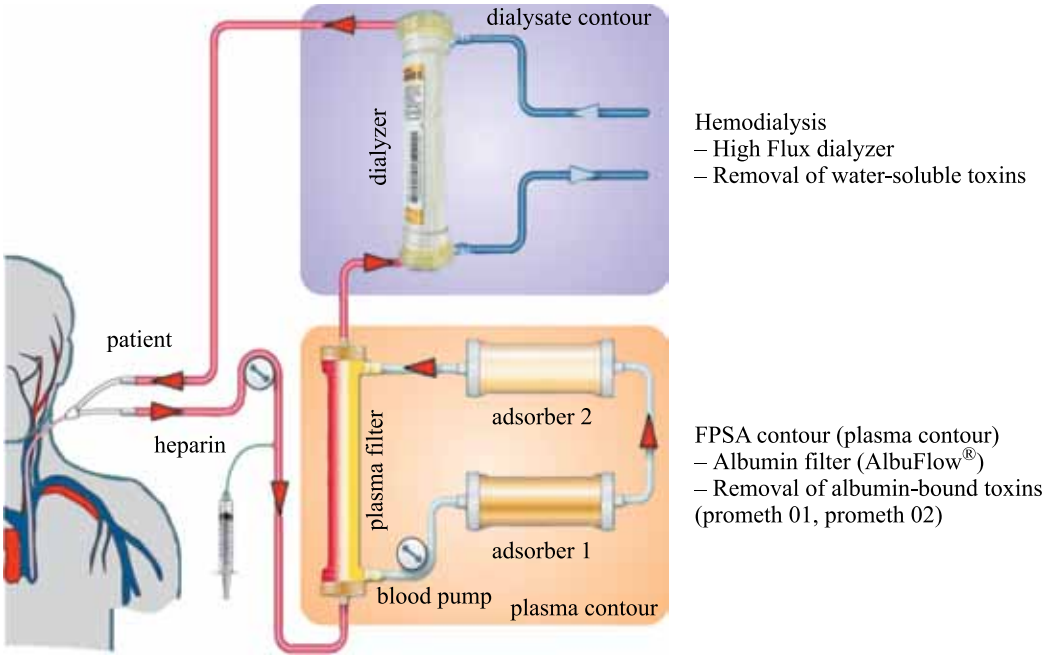

Fig. 1. Prometheus albumin dialysis. Schematic diagram of the extracorporeal circulation circuit [10]

Table 1

Baseline characteristics of patients

Parameters	No indications for FPSA, n = 134	Performed FPSA, n = 5	p
Age, years, mean ± SD	4.2 ± 5.1	12.4 ± 3.4	0.004
Gender, n (%)			0.661
Female	73 (54.5)	2 (40)	
Male	61 (45.5)	3 (60)	
Weight, kg, mean ± SD	17.6 ± 17	50.2 ± 17.7	0.014
PELD/MELD, mean ± SD	18 ± 9.9	34.2 ± 9.6	0.017
Encephalopathy, grade, n (%)			0.000
0–II	134 (100)	–	
≥III	–	5 (100)	
Diagnosis			–
Biliary atresia	47 (35.1)	–	
PFIC	14 (10.4)	–	
Biliary hypoplasia	12 (9.0)	–	
FCC	12 (9)	–	
Cirrhosis, undefined	11 (8.2)	3 (60)	
AIH	6 (4.5)	1 (20)	
PSC	5 (3.7)	–	
Wilson disease	4 (3)	1 (20)	
Graft disfunction	4 (3)	–	
Mucoviscidosis	4 (3)	–	
Alagille syndrome	3 (2.2)	–	
Glycogenosis	2 (1.5)	–	
Primary hyperoxaluria	2 (1.5)	–	
Tyrosinemia 1b	2 (1.5)	–	
Hepatoblastoma	1 (0.7)	–	
HCC	1 (0.7)	–	
Crigler-Najjer Syndrome, I	1 (0.7)	–	
Ketoacidemia	1 (0.7)	–	
Hemochromatosis	1 (0.7)	–	
Joubert syndrome	1 (0.7)	–	
GRWR %, mean ± SD	3 ± 1.3	2.1 ± 0.3	0.103
Transplant, n (%)			–
Full liver	5 (3.7)	3 (60)	
Left lobe	16 (11.9)	1 (20)	
LLS	91 (67.9)	–	
Right lobe	14 (10.4)	1 (20)	
Split-LLS	6 (4.5)	–	
Split-ERL	2 (1.5)	–	
Follow-up, months	9 ± 5.3	10.2 ± 4.2	0.583

Note. FPSA, Fractionated Plasma Separation and Adsorption; PELD, Pediatric End-Stage Liver Disease; MELD. Model of End-Stage Liver Disease; PFIC, Progressive familial intrahepatic cholestasis; FCC, Fibrocholangiocystosis; AIH. Autoimmune hepatitis; PSC, Primary sclerosing cholangitis; HCC, Hepatocellular carcinoma; GRWR, Graft-to-recipient weight ratio; LLS, Left lateral section; ERL, Extended right lobe.

observed at a bilirubinemia level of 350–872 with 597 ± 98 (μmol/L) average. The main laboratory parameters at admission are summarized in Table 2: marked hyperbilirubinemia, cytolytic syndrome, anemia, hypoproteinemia with low albumin levels, coagulopathy.

The number of FPSA sessions required to regress encephalopathy correlated with baseline bilirubinemia level. Thus, in a patient with a bilirubin concentration of 350 μmol/L, one session was sufficient, while a patient with a maximum level of 872 μmol/L needed three treatment sessions. The dynamics of the mean bilirubin concentration values during the FPSA treatment is shown in Fig. 2. At the end of the course of treatment, the mean bilirubin concentration decreased from 597 ± 98 to 236 ± 73 μmol/L. It should be noted that after the end of treatment, there was a tendency towards a regular increase in this parameter.

All five patients underwent liver transplantation within two to five days after FPSA treatment: in two cases, liver fragments were transplanted from live related donors, in three – from cadaver donors. The mean level of bilirubinemia before transplantation was 496 ± 108 μmol/L, while encephalopathy recurrence was not observed.

Of the technical complications during albumin dialysis, it is worth noting thrombosis of the extracorporeal circuit in one case, which was obviously associated with a low level of AT III (11%); in this case, an effective treatment session was performed after administration of two doses of fresh frozen plasma. The average heparin doses required for adequate anticoagulation in the extracorporeal circuit averaged 1122.2 ± 259.9 IU/h along the standard line before the plasma filter and 765.7 ± 287.2 IU/h along the additional line before the hemodialyzer. There were no clinical complications during the treatment sessions; hemodynamic parameters remained stable.

All patients were discharged from the clinic and are currently being followed up with functioning grafts.

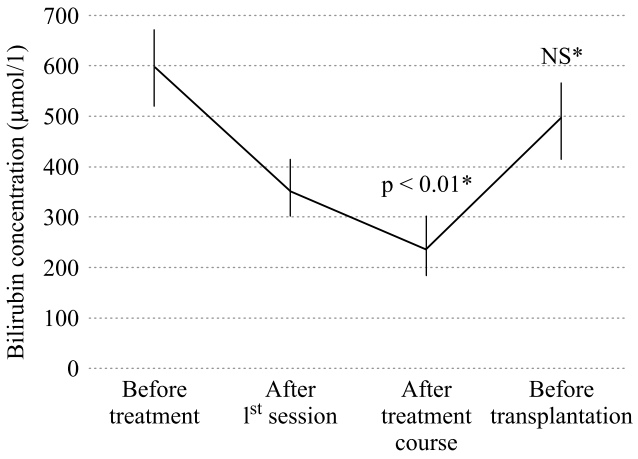

Fig. 2. Mean serum bilirubin change during FPSA sessions and before liver transplantation. * – compared to the concentration before treatment

Table 2

Characteristics of patients receiving FPSA

Parameters	n = 5
Age, years, mean ± SD	12.4 ± 3.4
Gender, n (%)	
Female	2 (40)
Male	3 (60)
Weight, kg, mean ± SD	50.2 ± 17.7
PELD/MELD, mean ± SD	34.2 ± 9.6
Laboratory indicators upon admission	
T. bil, μmol/l	553.6 ± 154.3
ALT U/L	193.2 ± 132.8
AST U/L	318.6 ± 158.5
Hb, g/L	73.2 ± 4.9
Total protein, g/L	63.6 ± 10.1
Albumin, g/L	29.0 ± 3.4
AT III,%	17.8 ± 11.5
PLT, 10^3/ μl	60.2 ± 27.5
PI, %	32.6 ± 11.0
APTT, C	58.0 ± 7.8
FPSA sessions, n, mean ± SD	2 ± 1
Complete encephalopathy regression with FPSA, n (%)	
Yes	60%
No	40%
Difference in total bilirubin level after FPSA session, μmol/L	
After 1st session (n = 5)	68.8 ± 159.9
After 2nd session (n = 5)	32.8 ± 89.4
After 3rd session (n = 1)	77
After 4th session (n = 1)	60
Survival,%	100
Follow-up after transplantation, months	10.2 ± 4.2

Note. PELD, Pediatric End-Stage Liver Disease; MELD, Model of End-Stage Liver Disease; T. bil., Total bilirubin; ALT – Alanine aminotransferase; AST, Aspartate aminotransferase; Hb, Hemoglobin; AT III, Antithrombin III; PI – Prothrombin index; APTT – Activated partial thromboplastin time.

DISCUSSION

Albumin dialysis systems aimed at maintaining liver function, and in particular the FPSA system, have been used in clinical practice for over twenty years. Already in the first studies, the ability of FPSA was shown to significantly reduce the concentrations of bilirubin, bile acids, and ammonia [11]. In subsequent studies, the effectiveness of the system was confirmed: there was a decrease in the activity of transaminases [12], as well as the concentration of amino acids [13], including those involved in the development of hepatic encephalopathy. The number of studies evaluating the clinical efficacy of FPSA is extremely limited. There are indications of regression of encephalopathy when using the system [14] and optimization of hemodynamic parameters [15]. In two studies evaluating the effectiveness of treatment by endpoints, there was no significant reduction in mortality with the FPSA [16, 17]. Moreover, a large randomized controlled trial in which FPSA was compared with standard therapy was terminated early [17], and only further analysis of patient subgroups revealed an improvement in the survival of the most severe patients with the use of FPSA. Such results can be explained by the extreme heterogeneity of the patients involved in the research and the lack of clear recommendations for therapy and its programs.

The present study, which used FPSA as a bridge to liver transplantation, came to quite encouraging results. Treatment courses, the duration of which was determined by the initial bilirubin concentration, made it possible to significantly reduce bilirubinemia and achieve a clear regression of encephalopathy. Interesting is the fact that at the end of treatment there was a regular increase in the level of bilirubinemia in the absence of encephalopathy recurrence. A plausible explanation for this phenomenon can be found in the literature. Thus, in the model of hepatic encephalopathy, a significant decrease in intracranial pressure was noted after FPSA sessions [18], which may contribute to the persistence of the clinical effect. In the present series of observations, the maximum period after the end of the course of treatment before liver transplantation did not exceed five days; possibly, with a longer waiting time for transplantation, it may be necessary to resume therapy.

CONCLUSION

The FPSA albumin dialysis system is an effective and safe method of preparing for transplantation in patients with terminal liver failure. If there is a real prospect of liver transplantation, this technique can be considered as lifesaving. Further research is needed to clarify the indications for initiating therapy and working out treatment programs when prolonging the waiting time for a transplant.

The authors declare no conflict of interest.

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