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# The effect of using the algorithm of restrictive intraoperative fluid therapy, early immune enteral nutrition, and early patient mobilization on orthotopic liver transplantation outcomes

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*Major surgical procedures induce a number of pathophysiological responses, which may lead to a significant increase in perioperative complications, delayed recovery and rehabilitation, and longer hospital stays. Fast-track surgery, also known as enhanced recovery after surgery (ERAS) or as multimodal surgery, aims at decreasing the rate of postoperative complications, creating optimal conditions for earlier postoperative recovery and return to normal life activities.*

*The implementation of fast-track programs results in a reduced treatment duration without increase in readmissions. In this article, we have described our experience in the application of fast track program components to improve the outcomes after liver transplantation.*

**Keywords:** fast-track surgery, enhanced recovery after surgery, liver transplantation.

## INTRODUCTION

Liver transplantation (LT) is a traumatic abdominal surgery with high perioperative risks. The latter can be related to both the surgical technique, and the specific problems caused by the severity of patient's baseline condition, and by the transplanted graft quality. [1]

The search of ways to minimize the negative effects of surgical trauma has been a central objective in many studies and research being conducted in the field of clinical anesthesiology and intensive care, surgery, and perioperaive pathophysiology [2]. Evidence-based strategies of enhanced postoperative recovery, as described in the so-called fast-track protocols, are aimed at creating the conditions to actualize the physiological potential of organ stability after a direct and indirect injury as a result of surgery. In practice, the creation of these conditions refers to limiting the traumatic impact of surgical intervention and, consequently, to preventing postoperative complications, and ensuring a rapid postoperative recovery of the patient. Enhanced postoperative recovery techniques in liver transplantation have not been worked out yet.

Among the components of modern fast-track protocols with proven efficacy in other less traumatic branches of clinical surgery, a special attention in liver transplantation surgery should be directed to the restrictive infusion-and-transfusion therapy and the improvement of patient nutritional status.

The aim of the study was to assess the effect of a complex restrictive fluid therapy guided by central hemodynamics monitoring, an early immune enteral nutrition, and an early patient mobilization on the postoperative course, complication rates, and outcomes after orthotopic LT (OLT).

## MATERIAL AND METHODS

Our work was based on a single-center, prospective, randomized, double-blind study.

The inclusion criteria were: the age over 18 years, the end-stage liver disease, the graft received from a brain-dead donor compatible by ABO blood group. Exclusion criteria were liver retransplantation, a fulminant liver failure, a significant hepatic dysfunction scored 20 or higher by Model For End Stage Liver Disease (MELD) scale, a significant renal function impairment expressed as End-Stage Kidney Disease (ESKD) of stage 3 or more, significant impairments in cardiovascular system assessed as Class III and over by NYHA (New York Heart Association), an uncontrolled infection, active bleeding from the upper gastrointestinal tract, an acute peptic ulcer.

In total, the study included 45 patients aged from 28 to 62 years who underwent OLT. Subsequently, 5 patients were withdrawn prematurely from data analysis because of the study protocol non-compliance and/or data missing.

Indications for OLT included either end-stage liver cirrhosis as the outcome of viral hepatitis B or C, or cryptogenic cirrhosis due to metabolic disorders and autoimmune hepatitis.

The patients were randomized into two groups: the comparison group (Group 1) where the enhanced recovery program was not used, and the study group (Group 2) that included the patients who underwent a complex of fast-track programme measures (Fig. 1). The randomization sequence was computer-generated and concealed in numbered opaque sealed envelopes.

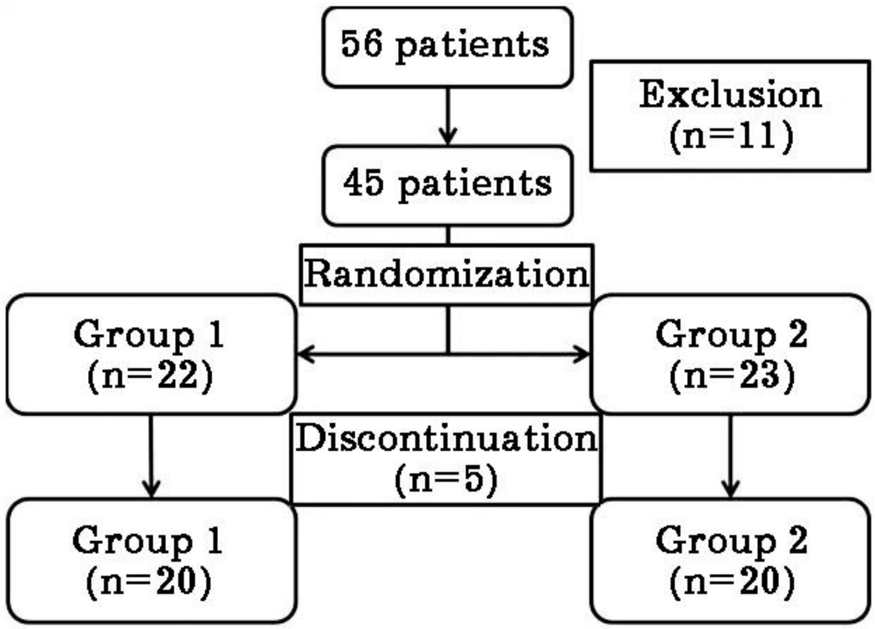


**Fig. 1. Inclusion of patients in the study: the study group (Group 2) and the comparison group (Group 1)**

The demographic data analysis demonstrated no statistical differences in main characteristics between the patients of two groups: gender and anthropometric parameters, baseline nutritional status, and baseline muscle strength. There were no differences between the groups in severity assessments of liver cirrhosis at baseline, and in basic parameters of nutritional status (blood-measured prealbumin and transferring levels) (Table 1).

**Table 1. Baseline characteristics of recipients from Groups 1 and 2**

| | Group 1 | Group 2 | P-value |
|---|---|---|---|
| Gender, male/female | 8/12 | 12/8 | 0.343 |

| | | | |
|---|---|---|---|
| Age, median (min-max), years | 53 (47-56) | 52 (47-58) | 0.729 |
| Body weight, median (min-max), kg | 76 (58-94) | 80 (56-98) | 0,372 |
| MELD, median (Min-max) | 16 (12-19) | 14 (11-16) | 0.394 |
| ASA*, III/IV | 15/5 | 16/4 | 0.456 |
| HRS**% | 15 | 7 | 0.693 |
| Bleeding,% | 23 | 19 | 0.273 |
| Ascites, % | 30 | 35 | 0.826 |
| Total protein, g/L | 64.3 (52.9-72.4) | 66.2 (55.2-76.1) | 0.448 |
| Albumin, g/L | 29.7 (24.9-37.7) | 31.3 (25.3-39.2) | 0.505 |
| Prealbumin, g/L | 7.9 (6.5-11.3) | 9.2 (5.8-13.5) | 0.477 |
| Transferrin, mcg/dL | 194 (161-203) | 206 (129-228) | 0.363 |
| Muscle strength, dyn | 37 (32-40) | 38 (30-42) | 0.603 |

Note: * ASA (American Society of Anesthesiologists); the system of classification of physical status before surgery; ** HRS - hepatorenal syndrome

All patients underwent a standard preoperative evaluation procedure that included a joint examination by a surgeon and an anesthesiologist, initial laboratory tests, signing an informed consent.

After the induction of anesthesia in the operating room, the catheterization of the superior vena cava and the radial artery were performed in all patients for monitoring the central venous pressure and invasive arterial pressure. The patients of the study group (Group 2) underwent a femoral artery catheterization for being connected to the unit for measuring central hemodynamics and volaemia by means of transpulmonary thermodilution technique using PiCCO-plus device (PULSION Medical Systems SE, Germany).

The intravenous fluid therapy was based on the established algorithm implying a restrictive fluid therapy regimen with monitoring the central hemodynamics and volaemia by means of transpulmonary thermodilution technique (Fig. 2). The type of colloid solution was chosen considering the current clinical situation. Either of the following could be used as colloid: fresh frozen plasma (FFP), a 4% gelatin solution, or an albumin solution.

The Program of enhanced recovery after surgery was used in the patients of the study group in the postoperative period. The comparison group management followed conventional approaches (Annex 6 to the Republic of Belarus Healthcare Ministry Order No. 6 of 05.01.2010).

The Program of enhanced recovery after surgery included the rejection of a long preoperative fasting, the prevention of postoperative nausea and vomiting syndrome, the removal of nasogastric tube on the operating table or on the first days after OLT, an early postoperative mobilization of patients (sitting down in bed, and in a chair on postoperative day (POD) 0, patient verticalization on POD 1, the start of rehabilitation exercises from POD 1), early enteral nutrition in the first 24 hours after surgery, the use of immune nutritive formula during the initial 3 days after surgery. As a basic enteral nutritional therapy, we used the immune nutritional formula containing arginine, omega-3 polyunsaturated fatty acids (PUFA), and dietary fibers (the "Impact® Oral" formula" manufactured by Nestle, Switzerland, 400-600 mL/day).

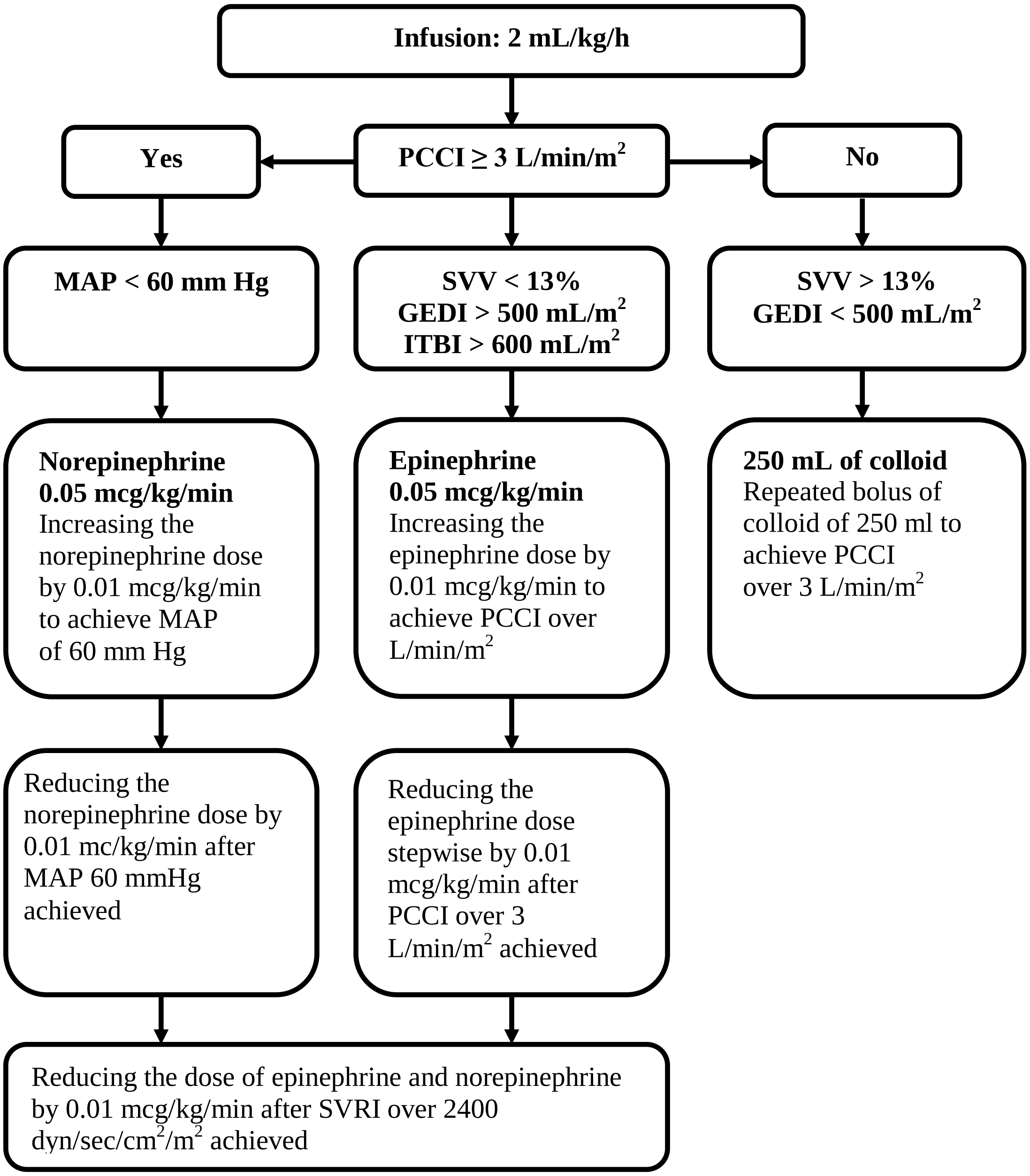


**Fig.2. Algorithm of restrictive perioperative fluid therapy in liver transplantation**

Note: PCCI: Pulse Contour Cardiac Index; MAP: Mean Arterial Pressure; SVV: Stroke Volume Variation; GEDI: Global End-Diastolic Volume Index; ITBI: Intrathoracic Blood Volume Index; SVRI: Systemic Vascular Resistance Index.

Comparisons between two groups were made considering the following parameters: recipient demographics (the gender, age, height, weight, body mass index, MELD score), donor demographics (the age, cause of death), graft characteristics (a total ischemia duration, a cold ischemia duration), preoperative clinical data (the cause of liver failure, cirrhosis complications, medical comorbidities, the drugs taken, a comprehensive clinical and laboratory assessment), intraoperatively measured parameters (invasive arterial pressure, central venous pressure, the volume of infusion and blood loss, catecholamine doses), laboratory parameters assessing the nutritional status (blood levels of prealbumin, transferrin) before surgery, on POD 0, 5, and 21 (or on the day of discharge from hospital), the postoperative morbidity, mortality, the length of stay in ICU, and a total hospital length of stay for a patient. Quantitation of serum prealbumin concentration was made using a "Konelab 30i" automatic biochemical analyzer (Thermo Fisher Scientific Co., USA) and the Prealbumin reagent kit (DiaLab, Austria).

Serum transferrin concentrations were measured by turbidimetric immunoassay on an Architect s8000 automatic biochemical analyzer (Abbott Laboratories, US), using a kit reagent Transferrin TRF (Abbott Laboratories, USA).

The patient muscle strength was measured by means of an electronic hand dynamometer DMER-120-0.5 (measuring range 2-120 daN); each assessment included three measurements of muscle strength on the dominant hand followed by the calculation of the mean value.

The study endpoints were the following: the blood loss and the volume of transfused major blood components, blood levels of transferrin and prealbumin at day 5 and 21 after surgery, the length of stay in the Intensive Care Unit (ICU) and in hospital, complication and mortality rates.

Statistical analysis was performed using STATISTICA 8 software package for Windows.

## STUDY RESULTS

### Restrictive infusion therapy

The total amount of intraoperative infusion in the patients of the study group was 4595.9 ± 1674.1 ml that was significantly lower than in the comparison group: 6499.1 ± 1889.9 ml (Mann-Whitney; $p < 0.01$ ). The same trend in the volume of infusion was observed at hepatectomy stage: 1226.8 ± 505.1 ml in the study group versus 2532.1 ± 1050.6 ml in the comparison group (Mann-Whitney; $p < 0.01$). The between-group analysis of the fluid therapy components showed a statistically significant difference in the amount of crystalloid solutions at hepatectomy stage 346.2 ± 225.9 ml in the study group vs. 621.4 ± 361.5 ml in the comparison group (Mann-Whitney; $p=0.04$). Meanwhile, there were no statistically significant differences between the groups in the total amount of crystalloid solution infused throughout the surgery (773.1 ± 479.8 ml in the study group vs. 601.9 ± 871.9 ml in the comparison group; Mann-Whitney; $p=0.73$); in the amounts of colloids infused at hepatectomy stage (720 ± 433 ml in the study group, and 1035.7 ± 414.4 ml in the comparison group; Mann-Whitney; $p=0.12$); and in the amounts of colloids infused throughout the surgery (1615.4 ± 650.4 ml in the study group, and 1718 ± 875 ml in the comparison group (Mann-Whitney; $p=0.98$).

The analysis of norepinephrine doses used revealed a statistically significant difference between the groups (0.031 ± 0.026 g/kg/min in the study group vs. 0.098 ± 0.066 g/kg/min in the comparison group; Mann-Whitney; p<0.01) (Table 2).

**Table 2. Patient management during the surgical intervention**

| Characteristics | Group 1 | Group 2 | P-value |
|---|---|---|---|
| Duration, median (min-max), min | 495 (250-660) | 505 (360-690) | 0.84 |
| Crystalloids, mean (SD), ml | | | |
| hepatectomy | 621.4 (361.5) | 346.2 (225.9) | 0.04 |
| ….overall | 871.9 (601.9) | 773.1 (479.8) | 0.73 |
| Colloids, mean (SD), ml | | | |
| hepatectomy | 1035.7 (414.4) | 720 (433) | 0.12 |
| ….overall | 1718 (875) | 1615.4 (650.4) | 0.98 |
| Infusion volume, mean (SD), ml | | | |
| hepatectomy | 2532.1 (1050.6) | 1226.8 (505.1) | <0.01 |
| overall | 6499.1 (1889.9) | 4595.9 (1674.1) | <0.01 |
| Norepinephrine, mean (SD), mcg/kg/min | 0,098 (0.066) | 0,031 (0.026) | <0.01 |

Note: SD: standard deviation

The analysis of intraoperative blood loss demonstrated statistically significant differences in the blood loss volume both at hepatectomy stage (323.1 ± 191.1 ml in the study group vs. 896.4 ± 303.5 ml in the comparison group; Mann-Whitney; p <0.01), and throughout the surgery (865.4 ± 570.6

ml in the study group vs. 1725.7 ± 750.8 ml in the comparison group; Mann-Whitney; p <0.01). The groups also significantly differed in the transfused amounts of fresh frozen plasma (FFP) (576.9 ± 480.5 ml in the study group vs. 1590 ± 895.2 ml in the comparison group; Mann-Whitney; p <0,01 ), autologous erythrocytes (261.8 ± 109.3 ml in the study group vs. 541.9 ± 428 ml in the comparison group; Mann-Whitney; p <0.01 ), packed red blood cells (384.8 ± 293.3 ml in the study group vs. 562 ± 422 ml in the comparison group; (Mann-Whitney; p=0.02 ), and cryoprecipitate (245.7 ± 173.1 ml in the study group vs. 478.1 ± 346.9 ml in the comparison group; Mann-Whitney; p = 0.01) ( Table.3).

**Table 3. Evaluation of Algorithm efficacy**

| Characteristics | Group 1 | Group 2 | P-value |
|---|---|---|---|
| Blood loss, mean (SD), ml | | | |
| hepatectomy | 896.4 (303.5) | 323.1 (191.1) | <0.01 |
| overall | 1725.7 (750.8) | 865.4 (570.6) | <0.01 |
| FFP, mean (SD), ml | 1590 (895.2) | 576.9 (480.5) | <0.01 |
| Autologous red blood cells (RBCs), mean (SD), ml | 541.9 (428) | 261.8 (109.3) | <0.01 |
| Packed RBCs, mean (SD), ml | 562 (422) | 384.8 (289.3) | 0.02 |
| Cryoprecipitate, mean (SD), ml | 478.1 (346.9) | 245.7 (173.1) | 0.01 |

**Nutritional status of patients**

Analyzing the changes in the blood level of transferrin over time (Table 4), we found its statistically significant decrease on POD 0 against preoperative baseline in both groups: 135 (118; 168) mg/dL on POD 0 vs. 206 (129; 228) mg/dL preoperatively in the study group (Mann-Whitney; p <0.05), and 107 (94; 138) mg/dL on POD 0 vs. 194 (161; 203) mg/dL preoperatively in the comparison group (Mann-Whitney; p <0.05).

**Table 4. Comparison of transferrin blood levels between groups 1 and 2**

| Transferrin mg/dL | Group 1 | Group 2 | P-value |
|---|---|---|---|
| Before surgery | 194 (161-203) | 206 (129-228) | 0.363 |
| POD 0 | 107 (94-138) | 135 (118-168) | 0.112 |
| POD 5 | 140 (91-171) | 177 (152-221) | 0,033 |
| POD 21 | 218 (167-246) | 214 (187-248) | 0.695 |

The transferrin levels were further tending to return to normal: transferrin was 177 (152; 221) mg/dL in the study group at POD 5, and 218 (167; 246) mg/dL in the comparison group at POD 21 (Fig. 3).

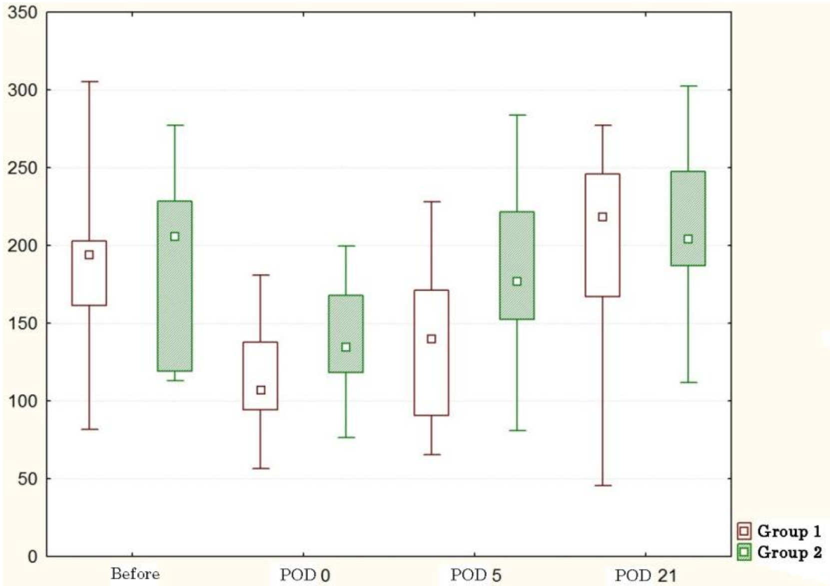


**Fig. 3. Changes of transferrin blood level over time in groups 1 and 2**

Studying the changes in blood level of prealbumin over time (Table 5), we saw a statistically significant increase and return to normal values showing 22.5 (17.4; 28.8) mg/dL in the study group at POD 5 vs. 9.2 (5.8; 13.5) mg/dL preoperatively (Mann-Whitney; p <0.05), and 18.3 (11.3; 22.3) mg/dL in the comparison group at POD 21 vs 7.9 (6.5; 11.3) mg/dL preoperatively (Mann-Whitney; p <0.05) (Fig.4).

**Table 5. Comparison of prealbumin blood levels between groups 1 and 2**

| Prealbumin, mg / dl | Group 1 | Group 2 | P-value |
|---|---|---|---|
| Before surgery | 7.9 (6.5-11.3) | 9.2 (5.8-13.5) | 0.477 |
| POD 0 | 10.0 (7.7-11.8) | 11.9 (8.1-16.2) | 0.449 |
| POD 5 | 15.3 (10.0-19.1) | 22.5 (17.4-28.8) | 0.048 |
| ACT 21 | 18.3 (11.3-22.3) | 20.6 (18.0-29.9) | 0.125 |

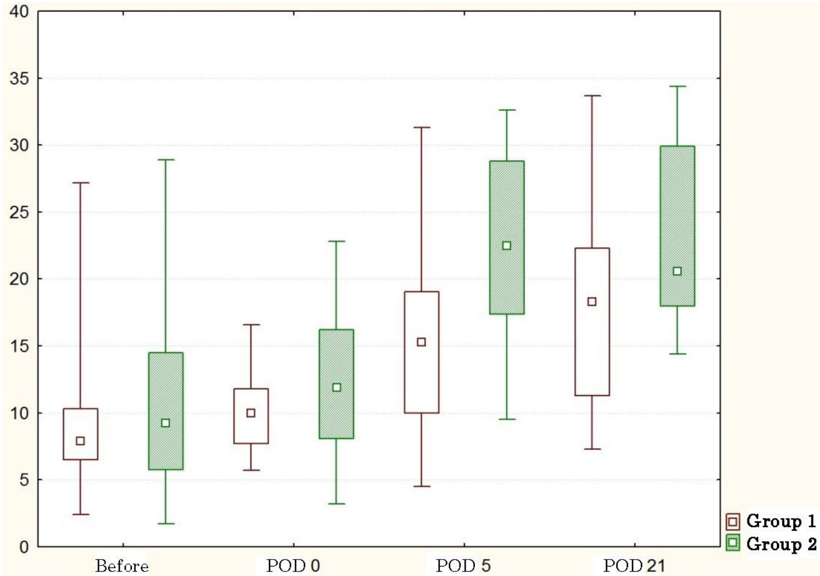


**Fig. 4. Changes of prealbumin blood level over time in groups 1 and 2**

The efficacy of the enhanced recovery program was also assessed by studying the changes of patient muscle strength over time (Table. 6). The analysis of the latter demonstrated a statistically significant reduction in the muscle strength in the patients of the comparison group from 35 (32; 45) dyne preoperatively to 28 (24; 34) dyne at POD 5 (Mann-Whitney; $p<0.05$); no significant reduction occurred in the study group demonstrating values from 37 (31; 45) dyne preoperatively to 35 (30; 43) at POD 5 (Mann-Whitney; $p = 0.909$) (Fig. 5).

**Table 6. Comparison of muscle strength between groups 1 and 2**

| Muscle strength, dyn | Group 1 | Group 2 | P-value |
|---|---|---|---|
| Before surgery | 35 (32-45) | 37 (31-45) | 0.969 |
| POD 5 | 28 (24-34) | 35 (30-43) | 0.041 |
| POD 21 | 36 (31-42) | 37 (31-43) | 0.909 |

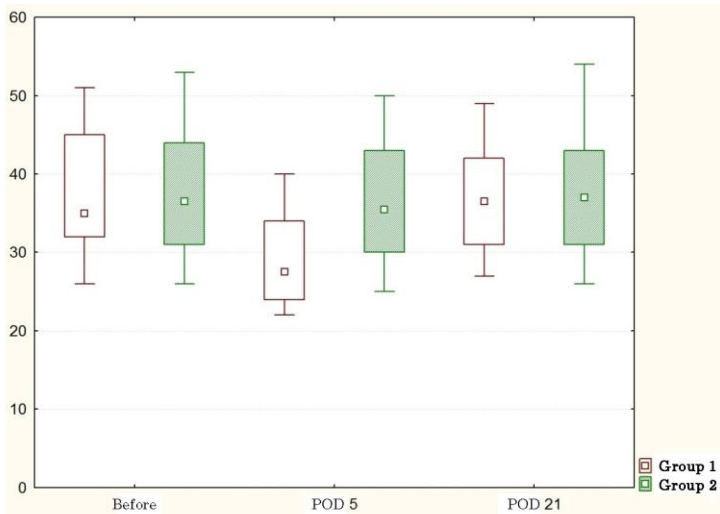


**Fig. 5. Changes of skeletal muscle strength over time in groups 1 and 2**

**Hospitalization outcomes and mortality**

Studying the patient treatment duration, we obtained the following results. The ICU length of stay was significantly decreased in the patients of the study group, making 70 (63; 96) hours vs. 120 (91; 288) hours in the comparison group (Mann-Whitney; p=0.015). A statistically significant reduction in the hospital length of stay was seen in the study group making 15 (13; 18) days versus 23 (17; 28) days in the comparison group (Mann-Whitney; p = 0.038) (Table. 7).

**Table 7. Comparison of treatment results between groups 1 and 2**

| Characteristics | Group 1 | Group 2 | P-value |
|---|---|---|---|
| Length of stay in ICU, hours | 120 (91-288) | 70 (63-96) | 0,015 |
| Length of stay in hospital, days | 23 (17-28) | 15 (13-18) | 0,038 |
| Incidence of infectious complications, % | 35 (7 of 20) | 10 (2 of 20) | 0.058 |
| Mortality, % | 15 (3 of 20) | 0 (0 of 20) | 0.072 |

Data analysis also showed a tendency to a decreased rate of infectious complications in the study group making 10% (2 of 20) vs. 35% (7 of 20) in the comparison group (Mann-Whitney; $p = 0.058$), and the mortality was zero (0 of 20) in the study group compared to 15% (3 of 20) mortality rate in the comparison group (Mann-Whitney; $p=0.072$).

## DISCUSSION

Fifty two years have passed since the first LT performed by Thomas Starzl. More than 500,000 such operations have been performed since then. An annual number of LTs performed in the world is increasing. According to WHO reports, more than 25,000 LTs were made in the world just for the year 2013 [3].

However, the complication rates and mortality after LT remain quite high and depend on the patient's age, the severity of cirrhosis, the occurrence and severity of complications, and the graft quality [4]. Currently, it is considered that the patient's nutritional status assessment and its timely improvement, an efficient analgesia in the perioperative period, the fluid therapy and transfusion, the blood loss and the volume of transfused blood components also have a considerable impact on the incidence of complications, and the liver transplantation outcome.

The above described components of anesthesia and perioperative intensive care are important interrelated parts of the complex multidisciplinary strategy aimed at reducing the number of complications in the perioperative period, and shortening hospital stays. According to literature reports, the set of measures established on the principles of evidence-based medicine was termed a "fast-track surgery", or the concept of enhanced recovery after surgery [5, 6].

Standard fast-track surgery protocols include up to 20 different pre-, intra-, and post-operative components, each of them having its clinical task that varies depending on the type of surgery and its surgical stress [7, 8]. The economic effect of the fast-track strategy aims at reducing the incidence of long and costly hospitalization associated with the need to treat postoperative complications.

Patients' tolerance to such traumatic surgical interventions can be explained by physiological characteristics, namely by a great functional reserve of the liver and its unique ability to regenerate. It has been established that the liver regenerates owing to hyperplasia and proliferation of remaining hepatocytes; and the maximum hepatocyte involvement in hyperplasia process occurs on the 1$^{st}$ day post-surgery, and the synthesis of transcription factors responsible for cell proliferation takes place as soon as at POD 2 [9].

The time frame dictates the need to use approaches that would prevent or minimize the impact of the factors impeding the liver tissue regeneration. In practice, these efforts aim at limiting the extent of surgical damage, preventing postoperative complications, and achieving a rapid postoperative recovery of the patient.

The concept of enhanced recovery in liver transplantation has a number of specific features related to the unique nature of this type of surgery. The largest European transplantation centers, such as University Clinics in Brussels and Hanover, Charité Clinic in Berlin, and King's College Hospital in London perform about 100 LTs annually [10]. The lack of randomized clinical trials (RCTs) to study the advantages of various approaches to anesthetic maintenance, perioperative intensive care, and the surgical technique of LT as well as a relatively low number of LT performed in smaller transplant clinics resulted in emerging diverse, and often conflicting strategies of perioperative patient management while performing LT. Thus, in today's world there is no center whose opinion would be exclusively recognized as the standard in all the above aspects. Meanwhile, large centers have demonstrated comparable data on morbidity, in-hospital mortality, one-year recipient and graft survival rates.

The lack of reliable evidence-base on the perioperative management of patients undergoing LT motivated us to find the ways of reaching the goals set by studying our own database. Today, our clinic has probably one of the largest retrospective databases of liver transplant recipients in Eastern Europe. It includes all the patients, starting from the first LT performed in the Republic of Belarus. Currently, our clinic database includes nearly 400 patients. In 2009, the Republic of Belarus joined the European Liver Transplant Registry (ELTR), the organization setting the standard requirements for objectivity and quality of the submitted information. Thus, the accuracy of the database is verified by the international auditing checks undertaken by ELTR on a regular basis.

The retrospective analysis of our database identified a number of factors in the fast-track programme that have a significant impact on the patient's course in the perioperative period, and on transplantation outcomes. These include: an early assessment of the patient's nutritional status and its timely improvement, a rapid postoperative mobilization of patients, a restrictive perioperative fluid therapy and the use of blood-saving technologies, an efficient analgesia in the perioperative period.

These factors were further modified with regard to anatomic and physiological characteristics of patients with liver cirrhosis, the aspects of surgical technique, the scenarios of LT postoperative course.

Fluid therapy in the patients of the study group was performed according to the restrictive protocol based on the originally-developed algorithm. The data analysis showed a statistically significant difference between the groups in the amount of infusion therapy both at hepatectomy stage (2532.1 ± 1050.6 ml in Group 1 vs. 1226.8 ± 505.1 ml in Group 2), and during the entire surgical intervention (6499. 1 ± 1889.9 ml in Group 1 vs. 4595.9 ± 1674.1 ml in Group 2).

The study results demonstrated a statistically significant reduction in the blood loss, the amount of transfused blood components and blood products in the study group compared to the group of patients who received the standard perioperative fluid therapy. The blood loss volume significantly decreased, almost three-fold at hepatectomy stage (896 ± 303.5 ml in Group 1 vs. 323.1 ± 191.1 ml in Group 2), and nearly by half in the entire surgery (1725.7 ± 750.8 ml in Group 1 vs. 865.4 ± 570.6 ml in Group 2) in the group of patients who were managed intraoperatively according to the algorithm of intraoperative fluid therapy in liver transplant recipients.

As a result of the reduced blood loss, a statistically significant reduction in the amount of transfused blood products and blood components was observed: a nearly three-fold reduction in the volume of the transfused FFP (1590 ± 895.2 ml in Group 1 vs. 576.9 ± 480.5 ml in Group 2); more than 50% reduction in the amount of packed red blood cells transfused (562 ± 422 ml in Group 1 vs. 384.8 ± 289.3 ml in Group 2); almost a two-fold reduction in the amount of the transfused cryoprecipitate (478.1 ± 346.9 ml in Group 1 vs. 245.7 ± 173.1 ml in group 2) in the group of patients whose intraoperative management was carried out according to the Algorithm. Moreover, the use of a restrictive approach based on the developed

Algorithm allowed the avoidance of blood transfusion in 5 liver transplant recipients from the study group.

A poor nutritional status of a patient before surgery has been proved to be an independent predictor of perioperative risk. It entails an increased incidence of postoperative complications, a delayed recovery, decreased survival rates [11]. Patients with a focal or diffuse end-stage liver disease in need of LT come to the clinic with a protein deficiency associated with the aggressive course of the disease. [12].

The nutritional status normalization and homeostasis correction in this patient population constitute an important part of perioperative management. A traumatizing surgical stress exacerbates a baseline loss of muscle mass in patients with liver failure [13]. According to other authors, an adequate correction of nutritional status via the enteral route using efficient nutrients can restore anabolic processes before and after surgery, and also provide for early recovery of gastrointestinal functions [14]. However, neither the initiation time and the duration of nutritional support, nor the optimal nutrient content and quantities have been standardized yet [15]. There is evidence that the so-called immunonutrition comprising omega-3 fatty acids, arginine, and nucleotides may optimize the management of patients with postoperative liver transplant dysfunction, and to enhance the recovery and healing process [16-18].

In our study, the nutritional support in the early post-OLT period was supplemented with a standard immune-enhanced formula. That accelerated the normalization of the clinical and laboratory parameters indicating the stabilization of a patient undergoing OLT. That was also suggested by the increments in blood levels of laboratory markers with short half-life (prealbumin, transferrin) in the study group at POD 5 ($p<0.05$). We should note that by measuring the changing concentrations of proteins: prealbumin, and transferrin synthesized in the liver, we could more accurately assess the synthetic function of the transplanted liver, and its recovery after surgery, since their blood levels reflect not only the nutritional status, but also the liver function. In addition to the above tests, the assessment of overall body muscle mass appeared in the study as an indirect marker of the patient nutritional status.

A statistically significant decrease in the muscle mass of the patients in the comparison group was seen by POD 5: from 35 (32; 45) dyn before surgery to 28 (24; 34) dyn at POD 5 (Mann-Whitney; $p<0.05$) that was not seen in the study group demonstrating 37 (31; 45) dyn before surgery vs. 35 (30 and 43) dyn at POD 5 (Mann-Whitney; $p = 0.909$).

Thus, we have proved a positive effect of immunonutrition both on the nutritional status of patients, and on the liver synthetic function.

The integral parameters suggesting the efficacy of the intraoperative fluid therapy algorithm, early immunonutrition, and early patient mobilization after OLT included shorter lengths of stay in the ICU, a decreased morbidity, and a lowered number of readmissions to ICU caused by a deteriorated patient condition. In the group of using the fast-track protocol, we documented a lower rate of pyo-septic complications vs. the comparison group (20% vs. 35%); there were statistically significant ($p <0.005$) reductions in the lengths of stay for the liver transplant recipients from the fast-track protocol group compared to the comparison group both in the ICU (70 [63-96] hours vs. 120 [91-288] hours), and in hospital (15 [13-18] days vs. 23 [17-28] days). A significant reduction in mortality rates was seen in the fast-track protocol group (0 vs. 15% in the comparison group).

Our study limitation was a small sample size that can be primarily explained by specific characteristics of this patient population and a relatively low number of such surgical operations.

The study has confirmed the hypothesis that the use of intraoperative fluid therapy algorithm, early immunonutrition, and early patient mobilization after OLT decrease postoperative morbidity and mortality rates, and significantly reduce the hospital lengths of stay. All these bring considerable medical and social benefits, and also can produce a direct economic effect.

**CONCLUSIONS**

1. The use of ERAS (or fast-track) complex protocol has proved its safety and efficacy while providing anesthesia and perioperative intensive care in adult patients undergoing OLT for hepatic failure assessed as Class A by Child-Pugh score and by MELD score under 20.

2. The developed Algorithm for a restrictive perioperative fluid therapy and transfusion used with the monitoring assessment of central hemodynamics and volemia as a component to ERAS programme were associated with over a two-fold decrease in the intraoperative blood loss and allowed the reduction in the number of transfusions.

3. The inclusion of early immunonutrition in the ERAS programme in OLT contributes to a more rapid recovery of the liver synthetic function and normalization of recipient's nutritional status.

4. The use of ERAS programme measures in the OLT perioperative period results in shortened lengths of stay in ICU and in hospital, and reduced complication rates.

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