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TREATMENT OF THE EARLY POSTOPERATIVE COMPLICATIONS FOLLOWING LIVER TRANSPLANTATION

ABSTRACT

Despite considerable reduction of the lethality rate after ortotopic liver transplantation and owing to the achievements in modern surgery, immunology and anesthesiology, the early postoperative complications still occur in nearly 70 % and can significantly compromise patient survival.

The aim of this study was to assess the frequency and causes of early post-transplantation complications and to develop effective means for their prophylaxis and treatment.

MATERIALS AND METHODS. Within the period from 03.04.2008 to 01.07.2014, altogether 260 liver transplantations were performed in 252 recipients in the Republican Center for organ and tissue transplantation (Minsk, Belarus: of them 209 (81.2 %) according to the classic technique, 46 (17.7 %) cavaplasty and 5 portal transposition (2.4 %). Thirty-six liver transplantations (13.9 %) were performed in children before 18 years of age. The strategy of peri-operative techniques and immune-suppressive therapy were the same for all patients.

RESULTS. Vascular complications occurred in 44 cases (16.9 %), biliary complications in 46 (17.7 %), acute kidney injury in 47 (18.1 %), primary non-functioning after 3 liver transplantations (1.2 %), early allograft dysfunction in 71 (27.3 %) cases, and bacterial complications after 66 (25.4 %) liver transplantations. Predictors of early allograft dysfunction were thermal ischemia and graft steatosis. Three-year patients' survival was 85 %.

CONCLUSION. The main cause of death was multiple organ failure developed in a sign of bacterial complications and early allograft dysfunction. Significant role in early postoperative complications prophylaxis acts interdisciplinary prevention of nosocomial infection.

KEYWORDS: liver transplantation; early postoperative complications; macrovesicular steatosis; warm ischemia time

During recent decades the problems of treatment of the patients with terminal stages of chronic diffuse and inherent metabolic diseases of the liver, primary and secondary malignancies of the hepato-biliary system as well as inherent anomalies of the bile-secreting pathways remain still topical in modern surgery of the abdominal cavity. Annually several million people, including individuals of workable age, die from these diseases worldwide [15]. Nowadays liver transplantation remains to be the only radical method in cure of such patients. Latest medical technologies and multi-disciplinary approach used during last decade allow reduce significantly the level of in-hospital lethality and increase survivorship after so complicated surgical intervention. Thus, the leading world centers have reported nearly 3-7 % of in-hospital post-transplantation lethality cases and 50-70 % of patients surviving for more than 10 years following liver transplantation [1, 4].

Despite the fact that major stages of liver transplantation were developed as far as in 1960-1980 years, it is still referred to one of the most complicated and traumatic surgical interventions in the abdominal cavity organs. This is linked both with technical difficulties in performance of complicated manipulations under 'inconvenient' conditions and with the conductance of anesthesiology and peri-operative intensive therapy in severely and extremely severe cases. Therefore a successful outcome of post surgery depends on the skill of the surgical and anesthesiology teams, on the one hand, and on the efficient prophylaxis and cure of post-operative complications [9].

As a rule, early post-operative complications develop during first two weeks and can be divided into three groups: (1) surgical, (2) somatic (caused due to infections) and (3) immunological **(Table 1)** [2].

The occurrence of such complications according to different research data vary in the range 20 to 70 %, depending on the quality of donor organ, preoperative patient's condition, experience of transplantation center team and surgery performance techniques [12].

In view of the circumstance that early postoperative complications produce essential influence on the cure results, we have put forward **the tasks**, first, to estimate the frequency and the causes of early post-operative complications following liver transplantation and, second, to elaborate effective approaches towards their prophylaxis and treatment.

MATERIALS AND METHODS

To achieve our goals we carried out one-center retrospective case-control study to investigate the incidence and causes of early post-operational complications in the Republican Scientific and Practical Center for Organ and Tissue Transplantation (Minsk, Republic of Belarus).

Our retrospective investigation included the results of 260 liver grafts performed between 03.04.2008 and 01.07.2014 in 252 recipients: 11 transplantations and 3 primary transplantations performed in other centers. Fourteen liver transplantations were performed from living relative donor, one split-live grafting and one combined liver-kidney transplantation. The number of children operations was 36 (13.9 %). Absolute majority of surgeries (operations, n = 209, 81.2 %) was performed according to the classic technique. The cava-cava plastics were made in 46 cases (17.7 %) and portal transpositions in 5 cases (2.4 %). Among cava-cava plastics, 20 of them were performed according to «piggyback» technique and 26 according to the method proposed by G. Belgitti. In 2013 we performed 66 operations for liver transplantation, all of them made in the above-mentioned Centre. So, this has approximated the level of nearly 7.0 per one million of the Belarus population. The main principles underlying intensive postoperative therapy were: prevention of hypothermia, routine administration of vasopressors (noradrenalin) and use of rapid infusion, limitation of crystalloids, refusal from dextrans, minimization of fluids mainly at the expense of the colloids (gelofusin and fresh-frozen plasma). The immune suppression strategy did not differ significantly from the commonly used one and consisted of induction by monoclonal antibodies (basiliximab) and postponed administration of the calcineurin inhibitors in the patients with a high risk of postoperative renal dysfunction.

Study was done for the incidence and causes of surgical (vascular and biliary) and somatic complications like bacterial, primary non-function and early dysfunction of liver graft as well as acute kidney injuries. Vascular complications were revealed by means of ultrasound duplex examination of liver hemodynamic and zone of vessel anastomoses proved by the results of spinal computed tomography in angio-mode or direct angiography.

Bile leakage at early postoperative period, the typical picture of anastomotic or non- anastomotic narrowing of the bile-secreting pathways diagnosed on retrograde cholangiopancreatography or magnetic resonance cholangiography served the criteria of biliary complications. If the results of biological liquid inoculation were positive, bacterial complication was registered [13-14]. The criterion of acute renal lesion was the need for renal replacement therapy [8]. Early transplant dysfunction was diagnosed based on the commonly accepted criteria: (1) total blood bilirubin of over 170 μmol/l on postoperative day 7 or (2) international normalized ratio (INR) of over 1.6 on postoperative day 7 or (3) aspartate and alanine aminotransferases levels of more than 2000 U/l during first postoperative week [10]. Primary nonfunctioning was diagnosed based on the absence of synthetic and detoxification functions of the liver immediately after operation (by lactate and urea levels, indices of hemostasis and liver enzymes) in the absence of other reasons (primarily vascular complications). In all these cases the primarily non-functioning transplant was the indicator for liver re-transplantation.

Table 1. Types of early postoperative complications following liver transplantation.

GROUPS	TYPES	OCCURRENCE, %
Surgical	Vascular	8-22
	Biliary	4-39
	Postoperative bleeding	10-15
	Non-specific (congenital ileus, postoperative wound suppuration)	10-21
Somatic	Early graft dysfunction	8-44
	Initial non-functioning graft	1-6
	Infection-caused	15-72
	Acute renal lesion	3-24
Immunological	Acute rejection (humoral and cellular)	10-30

In the course of our investigation we studied the factors of the appearance of these drastic complications based on the analysis of a number of pre- and postoperative parameters. The obtained data were interpreted for odds ratio (OR) and confidence intervals (CI) 95 % using of the Statistica 8 software.

RESULTS AND DISCUSSION

Vascular exacerbations developed after 44 liver transplantations (16.9 %), of which 29 (11.1 %) arterial and 15 (5.8 %) venous. Among arterial stenosis there prevailed stenosis of the anastomoses between donor's and recipient's artery 22/29 (75.9 %) which were diagnosed at various postoperative terms (from day 4 to 2 years). In 15 of 22 cases (68.2 %) critical stenosis was confirmed by angiography (more than 75 %) making us perform roentgen endovascular stenting of the site of stenosis **(Figure 1)**.

In none of the cases liver artery stenosis was accompanied with liver transplant dysfunction. Liver artery thrombosis occurred after 5 operations (1.9 %). All of the cases with arterial thrombosis were diagnosed at early postoperative period (from 12 hours to 5 days). In two cases we successfully performed roentgen endovascular stenting, in one case reanastomosis followed by stenting of the anastomosis area and in one case liver retransplantation. Arterial thrombosis was the cause of death in one patient (0.4 %). Steal-syndrome not diagnosed prior to operation was identified after two liver transplantations (0.8 %) on day 3 and 4 post transplantation and it was arrested via spleen artery embolization.

Portal vein stenosis prevailed among venous complications (11 of 15 patients, 73.3 %), being diagnosed by spinal computer angiography at patients' discharge from the hospital.

With the clinic of portal hypertension we performed anastomosis stenting in three patients. In one case (0.4 %) we diagnosed portal anastomosis thrombosis which was remedied within first 24 hours

during reoperation and after subsequent stenting. In three cases (1.2 %), within a period from two months to 3 years we diagnosed stenosis of the upper caval anastomosis after liver transplantation according to classical technique which was stopped in the course of stepwise balloon angioplasty.

Analysis has shown that neither donor's or recipient's age, nor time of overall, cold and thermal ischemia of the transplant, nor initial severity of the patients medical condition and intraoperative blood loss have produced any significant influence on the frequency of vessel exacerbations ($p > 0.05$). It is notably that great number of arterial stenosis 7 (31.8 %) developed after first 50 liver transplantations that is connected with mastering of methods of arterial anastomosis installing during work-out of the major stages of operation. The total number of arterial exacerbations diagnosed during first two weeks after liver transplantation made 17 (38.6 % of total number) and only in one case, despite timely diagnostic and surgical correction, they appeared to be the cause of lethal outcome post liver transplantation.

Thus, using commonly approved protocol for prophylactic of vascular complications with surgical optic and microscope during vessel's suturing, monitoring of coagulogram, main factors of coagulation and direct anticoagulants or desaggregants prescription at early postoperative period as well as dynamic ultrasound control of the zone of vascular anastomosis, timely roentgen endovascular correction of the detected deviations we have practically avoided such life-threatening complications as hepatic artery and portal vein thrombosis [6,7,11].

The biliary complications are "the Achilles' heel" in liver transplantation. In our series they developed after 46 operations (17.7 %).

Figure 1. Stenting of the hepatic artery stenosis after liver transplantation.

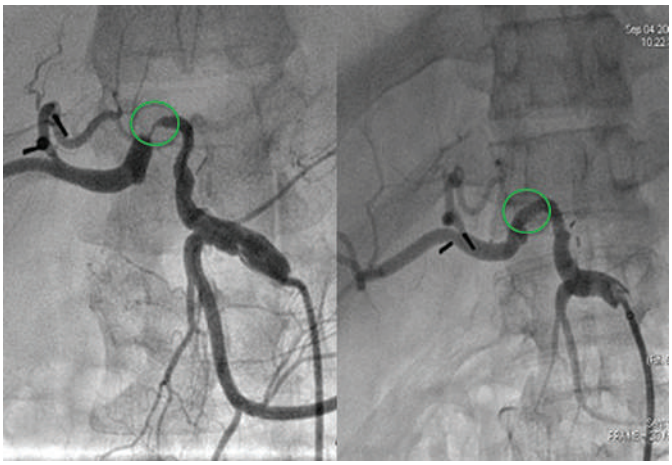
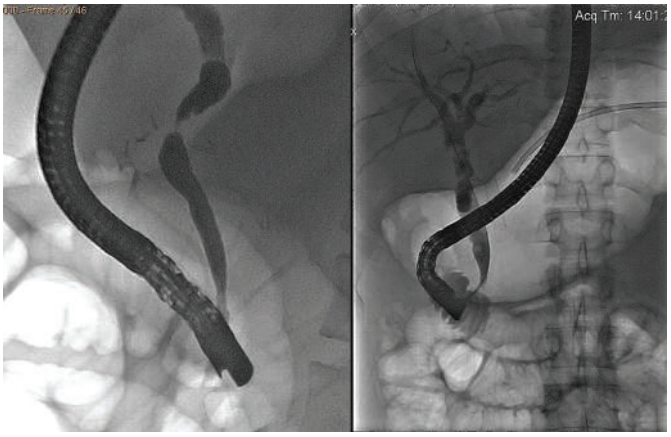


Figure 2. Endoscopic retrograde cholangiopancreatography, balloon dilatation and stenting of the biliary tract stricture.



When analyzing biliary complications we found that they appeared primarily at early postoperative period (42/46, 91 %). There prevailed anastomotic structures of the bilio-biliary anastomoses which appeared after 30 transplantations, 26 of which (86.7 %) appeared at early postoperative period. An absolute number of these complications (83.3 %) were arrested by using less invasive technologies (endoscopic transpapillary stenting) **(Figure 2)**.

In five patients (1.9 %) it was impossible to perform endoscopic dilation and stenting and therefore we made reconstructive operation that is performed choledocho-entero anastomosis on the Roux-en-Y loop of jejunum. We tried to postpone performance of reconstructive operation until stabilization of patient's condition, limiting the procedure to placing percutaneous transhepatic cholangiostoma.

Failure of the bilio-biliary anastomosis occurred after 8 liver transplantations (3 %) on day 1 to 13 post operations. All the patients were urgently operated. Bilio-biliary anastomosis reconstruction was made in two of them, created choledocho-entero anastomosis on the Roux-en-Y loop was done in four patients and performed of outer cholangiostoma was done two patients. Two of them (0.8 %), despite proper treatment, developed sepsis and multiple organ failure caused their death.

Another serious problem was the development in early postoperative period of the ischemic non-anastomotic-biliary structures (ITBL) **(Figure 3)** that can be assigned to bad quality of donor organ and its conditioning at the pre-transplantation stage.

In our series we diagnosed ITBL after 8 transplantations (3.1 %). Analysis has shown that their development correlated with donor's age – in the donors over 50 years they occurred significantly more often ($p = 0.02$). Correction of the given complication can be done by the way of stepwise balloon dilation of the narrowed sites (not always effective at times). In several cases we observed prolonged maintenance of intrahepatic cholestasis leading to the development of a secondary biliary cirrhosis after several years post operation.

Therefore at the stage of conditioning and during postoperative period a number of measures should be undertaken aimed at prophylaxis of ITBL development. Since 2013 year for prophylaxis of development of ischemic non-anastomotic biliary structures we have been using complex of treatment measures consisting of streptokinase injection during donor operation, washing biliary duct with saline (at room temperature) prior to flushing to prevent formation of bile casts and their toxic impact on the bile pathway epithelium and washing transplant liver artery under pressure 40-50 mm Hg during back-table surgery [3, 5]. Within a period from 01.01.2013 to 01.07.2014 years (99 transplantations) there was not a single case of this complication ($p = 0.0003$) after application of this prophylactic method.

Acute renal lesion developed at early postoperative period in 18.1 % cases (after 47 orthotopic liver transplantations) and needed 1 to 44 session of renal-replacement therapy (continuous prolonged

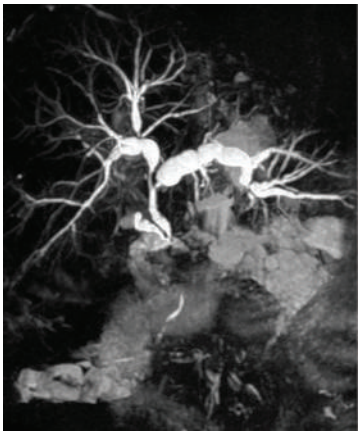


Figure 3. Ischemic non-anastomotic stricture biliary tract after liver transplantation.

hemodiafiltration). Against background of liver transplant dysfunction and chronic rejection, one patient displayed progression of renal failure and we performed liver re-transplantation and kidney transplantation after 11 months. The risk factors for a development of acute renal lesion were as follows: recipients' poor medical condition before operation, intra-operation blood loss, length of transplant thermal ischemia and its post-operative dysfunction as well as development of septic complications **(Table 2)**.

Primary non-functioning of the liver graft was diagnosed after 3 liver transplantations (1.2 %). Two patients underwent urgent liver re-transplantation with the following recovery of one of them. The lethality made 66.7 %. Thorough analysis did not reveal any statistically significant causes of appearance of this complication.

The frequency of early liver transplant dysfunction made 27.3 % cases (after 71 operations). The given complication was not infrequently accompanied with a development of septic complications that caused lethality at the hospital stage in the majority patients. Notably, the logistic regression method allowed find that independent predictors of early allograft dysfunction appeared to be the time of thermal ischemia and the degree of macrovesicular steatosis **(Table 3)**. According to the results of ROC-analysis, the area under characteristic curve for macro vesicular steatosis made 0.730 and the threshold meaning/value 15 % with sensitivity 52 % and specificity 81 %.

Bacterial complications developed after 66 orthotopic liver transplantations (25.4 %). Their most frequent stimulators were: *Enterococcus spp.* (4.5 %), *Pseudomonas aeruginosa* (33.3 %), *Acinetobacter baumanii* (33.3 %) and *Klebsiella pneumoniae* (22.7 %) which are sensitive predominantly to reserve antibiotics. The risk factors of development of bacterial complications were: early graft dysfunction, need for relaparotomy, intra-operative blood loss more than 2500 ml as well as post-operative acute kidney injury **(Table 4)**.

During in-hospital stay 16 of 252 patients died at different post-operative terms (from 18 hours to 108 days). The lethality made 6.35 %. Twelve patients (75 %) died from multiple organ failure syndrome against background of infection-caused complications and liver graft dysfunction. In the rest cases the cause of patients' death was: acute cerebral blood circulation disorder, liver artery thrombosis, primary non-functional graft and hemorrhagic shock. Within 75 months (more than 6 years) of the existence of liver transplantation program in Belarus, another 16 patients (6.35 %) died from various causes, predominantly progression of oncologic processes. Of July 1 2014 year, 220 (87.3 %) of 252 operated patients have survived. The estimated 3-year survivorship index for the recipients made 85 % **(Figure 4)**.

Table 2. Factors influencing acute renal injury at early postoperative period following liver transplantation.

FACTORS	ACUTE RENAL INJURY, (95 % CI), N = 47	NORMAL RENAL FUNCTION, (95 % CI), N = 213	P
MELD of the recipient	25 (17; 30)	16 (13; 21)	0.0001
Intraoperative blood loss, ml	1700 (1200; 3100)	1150 (650; 1700)	0.0005
Thermal ischemia, min	65 (55; 75)	58 (50; 65)	0.004
Presence of early transplant dysfunction	OR 3.5 to 1		0.0002
Presence of septic complications	OR 7.9 to 1		0.00000

Table 3. Predictors of early dysfunction of liver transplant.

PREDICTORS	OR (95 % CI)	P
Macrovesicular steatosis	23 (6.8; 54.3)	0,00001
Time of warm ischemia	12.9 (4.6; 29.7)	0.0003

Table 4. Risk factors of inflectional exacerbations at early postoperative period following liver transplantation.

FACTORS	OR 3.5 TO 1 (95 % CI)	P
Early dysfunction of liver transplant	2.2 (1.2; 4,0)	0.009
Intraoperative blood loss	6.8 (4.6; 16.7)	0.007
Acute liver injury	7.8 (3.3; 15.8)	0.00000
Relaparotomy	13.1 (6.1; 28.3)	0.00000

CONCLUSIONS

1. LIVER TRANSPLANTATION IS THE EFFECTIVE METHOD OF TREATMENT, ALLOWING RECEIVING GOOD EARLY AND REMOTE RESULTS IN TERMINAL STAGE OF VARIOUS LIVER DISEASES.
2. SUCCESSFUL PERFORMANCE OF THIS RATHER COMPLICATED SURGICAL INTERVENTION IS IMPOSSIBLE WITHOUT HIGHLY-QUALIFIED MULTI-DISCIPLINE TEAM CONSISTING OF THE SURGEONS, ANESTHESIOLOGISTS-REANIMATOLOGIST, PHYSICIANS OF LABORATORY DIAGNOSTIC, SPECIALISTS FOR ENDOSCOPY, ROENTGEN-ENDOVASCULAR SURGERY, ULTRASOUND AND RADIAL DIAGNOSTIC.
3. THE MAIN CAUSE OF DEATH AFTER LIVER TRANSPLANTATION IS THE MULTIPLE ORGAN FAILURE DEVELOPING AGAINST BACKGROUND OF INFECTION-CAUSED COMPLICATIONS AND LIVER GRAFT DYSFUNCTION.
4. A DECISIVE ROLE IN THE PROPHYLAXIS OF EARLY POSTOPERATIVE COMPLICATIONS IS ASCRIBED TO ORGANIZATION OF SANITARY-EPIDEMIOLOGIC MEASURES AND PROPHYLAXIS OF IN-HOSPITAL INFECTION WITH THE RESPONSIBILITY OF MEDICAL NURSE AND PHYSICIAN-EPIDEMIOLOGIST.
5. LONG-TERM SURVIVORSHIP OF PATIENTS IN LARGE MEASURE DEPENDS ON THE QUALITY OF OPERATIVE INTERVENTION AND PROPHYLAXIS OF COMPLICATIONS AT EARLY POSTOPERATIVE PERIOD.

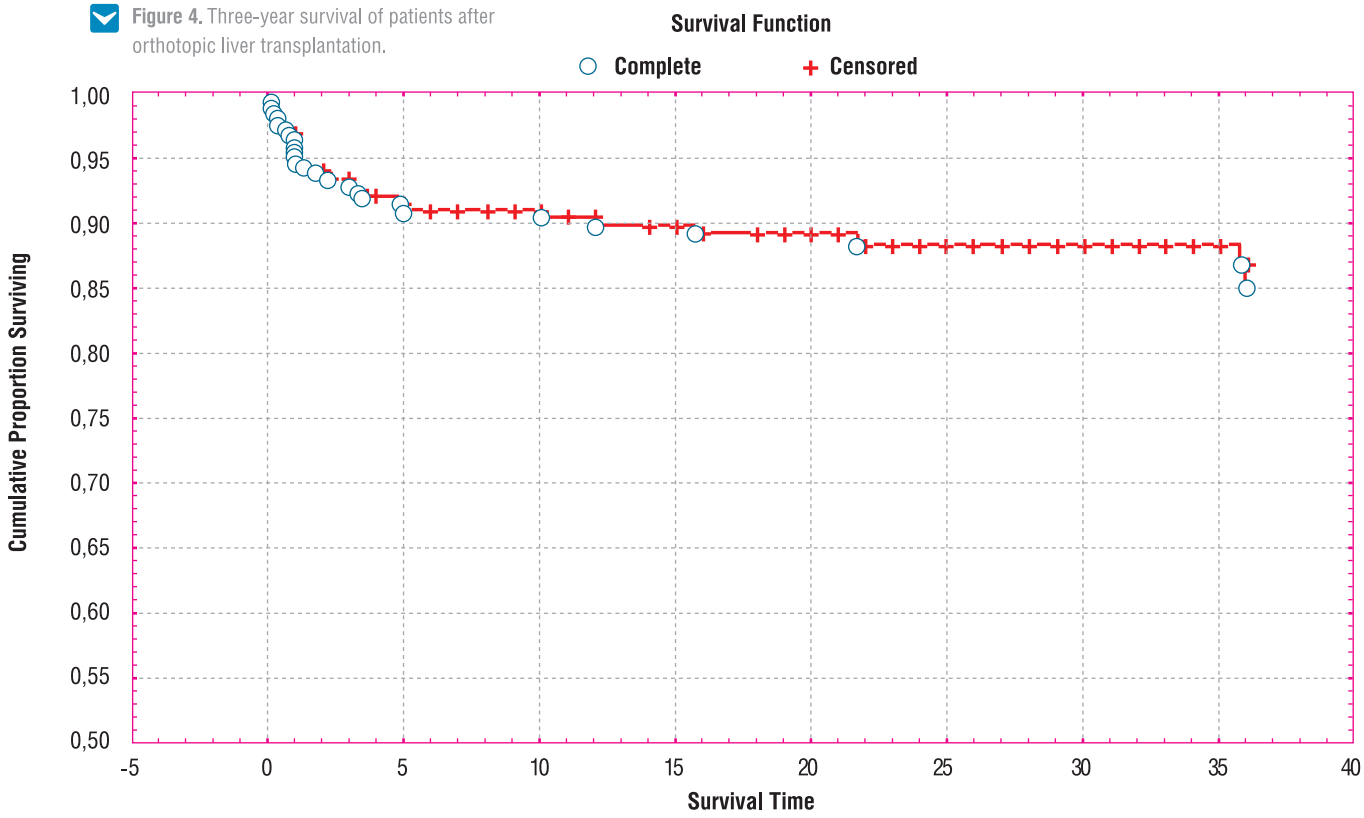


Figure 4. Three-year survival of patients after orthotopic liver transplantation.

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