DOI: 10.15825/1995-1191-2024-2-63-72

HYPOTHERMIC OXYGENATED PERFUSION IN LIVER TRANSPLANTATION FROM EXPANDED CRITERIA DONORS

A.V. Shabunin[1, 2], O.B. Loran[1, 2], D.Yu. Pushkar[1], E.I. Veliev[1], M.G. Minina[1, 3], P.A. Drozdov[1, 2], S.A. Astapovich[1], E.A. Lidzhieva[2]

[1] Botkin Hospital, Moscow, Russian Federation
[2] Russian Medical Academy of Postgraduate Education, Moscow, Russian Federation
[3] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

Objective: to improve the outcomes of liver transplantation (LTx) from expanded criteria donors (ECDs) through hypothermic oxygenated machine perfusion (HOPE). **Material and methods.** The study included 63 cases of LTx from suboptimal brain-dead donors. Group I (control) consisted of 34 persons in which liver transplant was preserved only by static cold storage (SCS), while group II (main) comprised 29 cases where *ex situ* HOPE was used after static preservation. We evaluated the efficacy and safety of the latter in a comparative clinical study and by studying ultrastructural changes in the liver using electron microscopy. **Results.** No statistically significant differences between the groups in terms of baseline characteristics of donors, recipients and several perioperative parameters ($p > 0.05$) were obtained. Peak aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in the first week after transplantation were 1,052 (IQR: 712–1,842) U/L and 1,213 (IQR: 613–2,032) U/L in the HOPE group, and 1,943 (IQR: 1,294–5,214) U/L and 2,318 (IQR: 1,032–6,219) U/L in the SCS group (control). The levels were statistically significantly lower ($p = 0.002$ and $p < 0.001$, respectively). Median comprehensive complication index (CCI) in the main and control groups was 0 (IQR: 0–22.6) and 27.6 (IQR: 0–100) respectively. The differences were statistically significant ($p = 0.001$). Similarly, statistically significant differences were noted in terms of recipient time in the intensive care unit (ICU) and overall length of hospital stay ($p = 0.042$ and $p = 0.028$) – they were less in the HOPE group. Electron microscopy evaluation of the morphology of liver grafts revealed that hepatocytes sustained less injury during HOPE. **Conclusion.** *Ex situ* HOPE is a safe and effective way of preserving liver transplants. Its use in LTx from expanded criteria donors can lessen the severity of ischemia-reperfusion injury (IRI) in the organ and enable additional assessment of the suitability of an organ for transplantation.

Keywords: liver transplantation, preservation, expanded criteria donors.

INTRODUCTION

Liver transplantation (LTx) is currently the only definitive treatment for patients with end-stage liver disease. From Thomas Starzl's initial successful series of transplants in the 1960s to the present, this method has quickly expanded throughout the world and has become a routine clinical practice in many surgical centers. The availability of transplant care directly depends on donor resources, which is in short supply worldwide. This inevitably leads to a higher number of waitlisted candidates and increased waitlist mortality. According to a 2022 study by Eurotransplant, waitlist mortality reached 33.9% in 2022, essentially unchanged from outcomes a decade ago [1].

The use of expanded criteria donors (ECDs) is an effective way to increase the availability of LTx, but it is associated with increased risk of adverse effects in the postoperative period. It is known that grafts obtained from suboptimal donors are more susceptible to ischemic injury during preservation and subsequent reperfusion injury in the recipient's body [2]. Severe ischemia-reperfusion injury (IRI) causes early allograft dysfunction (EAD) [3]. According to the results of a large study from Mayo Clinic, the incidence of EAD was 26.5% and its development had a statistically significant impact on both immediate LTx outcomes and long-term recipient survival [4]. In some cases, EAD may be irreversible, which corresponds to primary graft nonfunction (PNF), with mortality exceeding 50% [5].

It is possible to reduce IRI severity in particular by improving graft preservation conditions. Perfusion methods of liver preservation from ECDs in comparison have already proved their advantage over static cold storage in many studies [6–8]. For instance, according to a multicenter randomized trial, the use of hypothermic oxygenated machine perfusion (HOPE) in LTx from ECDs reduces the risk of EAD, early postoperative complications, and duration of hospital stay [7]. Never-

Corresponding author: Pavel Drozdov. Address: 15/8, Brusilov str., Moscow, 117148, Russian Federation. Phone: (962) 985-04-41. E-mail: dc.drozdov@gmail.com

theless, introduction of perfusion technologies into the clinical practice of transplant programs is still limited. Only a few centers in the Russian Federation routinely perform machine perfusion preservation of donor organs.

Since 2020, Botkin Hospital has been introducing and actively using various perfusion techniques used for preservation of solid organs [9–11]. In this study, we have analyzed the first results of HOPE application in LTx from suboptimal brain-dead donors.

MATERIAL AND METHODS

The study is based on analysis of the outcomes of treatment of 63 liver recipients operated at Botkin Hospital from 2018 to 2023. In all cases, an isolated whole LTx from a brain-dead expanded criteria donor was performed. Donor data were classified into expanded criteria risk factors as proposed by Eurotransplant. These are:

- Donor age >65 years;
- ICU stay >7 days;
- Body mass index (BMI) >30 kg/m^2;
- Macrovesicular steatosis >40%;
- Sodium >155 mmol/L;
- ALT >105 U/L, AST >90 U/L;
- Total bilirubin >3 mg/dL.

Group characteristics

Group I (control group) included 34 cases in which liver graft was preserved only by static cold storage. The median age of recipients was 49 (IQR: 26–54) years, and median BMI was 24 (IQR: 21.0–32.0) kg/m^2. Among all recipients, 21 (61.7%) were males and 13 (38.2%) were females. Median MELD score was 16 (IQR: 14–19). Donor age was 54 (IQR: 31–66) years and BMI was 29 (IQR: 24.0–35.0) kg/m^2. Median time in ICU was 78 (IQR: 25.0–137.0) hours. Vasopressor therapy with norepinephrine was administered in all (100%) donors, among them 13 (34.7%) had the dose exceeding 1000 ng/kg/min or a second vasopressor was used. Median serum sodium level was 148 (IQR: 134–155) mmol/L, AST and ALT were 44.0 (IQR: 24.0–79.0) and 59.0 (IQR: 26.0–142) U/L, respectively. Mild steatosis (<40%) occurred in 10 (29.4%) and moderate (40–60%) in 24 (70.6%) liver transplants.

Group II (main group) included 29 recipients whose LTx was followed by HOPE after static storage. In 7 cases, classic HOPE was performed exclusively via the portal vein, in 22 cases dual HOPE was carried out both via the portal vein and via the hepatic artery. Median age of recipients was 51 (IQR: 32–59) years and BMI was 25 (IQR: 23.0–32.5). There were 16 males (55.2%) and 13 females (44.8%). Median MELD score was 17 (IQR: 14–20). Donor age was 58 (IQR: 31–67) years, BMI was 29 (IQR: 25.0–33.0) kg/m^2, and median ICU time was 86 (IQR: 34.0–122.0) hours, respectively. Vasopressor therapy was administered in all (100%) donors, among them 13 (44.8%) had a norepinephrine dose exceeding 1000 ng/kg/min or a second vasopressor was used. Median serum sodium level was 152 (IQR: 137–159) mmol/L, AST and ALT were 43.0 (IQR: 32.0–77.0) and 59.0 (IQR: 22.0–82.5) U/L, respectively. Express or routine histological examination showed that mild steatosis (<40%) occurred in 9 (31%) and moderate (40–60%) in 20 (69%) liver transplants. Detailed comparative characteristics of the groups are presented in Table 1.

Liver transplantation and postoperative period

Surgical interventions for liver removal from a deceased donor were performed using standard conventional technique. In all cases, organs were preserved using Bretschneider's solution (Custodiol HTK). Liver transplantation in all cases was performed with preservation of recipient inferior vena cava and caval reconstruction using the Belghiti technique. The recipient was managed in the postoperative period according to standard protocols in accordance with the National Clinical Guidelines. Basiliximab 20 mg was used as induction immunosuppressive therapy, administered intraoperatively and on day 4 after transplantation. Immediately before reperfusion, methylprednisolone was administered intravenously at 10 mg per kg of the recipient's weight, with subsequent reduction of the daily dose and complete withdrawal on day 4. For the majority of recipients, maintenance immunosuppression consisted of extended-release tacrolimus monotherapy, the target level of which was maintained within 7–10 ng/mL.

IRI intensity was determined by the highest level of transaminases in the first week after transplantation. EAD was defined according to the criteria stipulated by Olthoff et al. [3] with at least one of the following laboratory characteristics:

- Total bilirubin ≥10 mg/dL (171 μmol/L) on day 7 postoperatively;
- International normalized ratio (INR) ≥1.6 on day 7 postoperatively;
- ALT or AST >2000 IU/mL within the first week after surgery.

Ex situ hypothermic oxygenated machine perfusion

HOPE was carried out in the operating room of the transplant unit (according to the back-to-base technique) using a heart-lung machine. The liver graft was aseptically removed from the transport container into the container with Bretschneider's preservative solution (Custodiol HTK) cooled to 4–10 °C; the portal vein and graft artery were cannulated (Fig. 1, a). In the classic version, only the portal vein was cannulated (Fig. 1, b).

The perfusion procedure was performed by means of two roller pumps, two perfusion circuits and one oxygenator. The volumetric flow rates, determined by

operation of the roller pumps, were selected by the operator to maintain a perfusion pressure of 5 mmHg for the portal system and 25 mmHg for the arterial system. The effluent flowing through the inferior vena cava into the container where the graft was placed was taken into the perfusion system by two cannulas fixed at the bottom of the container. A schematic representation of the dual liver perfusion system is presented in Fig. 2.

Perfusate temperature remained within 10 °C throughout the entire procedure. Laboratory perfusion parameters were monitored every 30 minutes: acid-base balance (with partial pressure of oxygen PaO_2 determined), AST and ALT. The target PaO_2 of the perfusion solution was maintained at 400–600 mmHg.

During perfusion, the graft was treated before transplantation and its arteries were examined for leaks. Just before the graft was to be immersed into the wound, machine perfusion was terminated at the end of the hepatectomy stage.

Morphological assessment of liver grafts during preservation

We carried out an electron microscopic study in order to determine the intensity of liver cell damage at the ultrastructural level under ischemic conditions, depending

Table 1

Comparative analysis of liver transplant outcomes depending on preservation method

Indicator	Subgroup I.I (SCS) n = 34	Subgroup II.I (HOPE) n = 29	Significance (p value)
Recipient characteristics			
Recipient age (years)	49 (IQR: 26–54)	52 (IQR: 31–58)	0.32
Recipient male gender (n, %)	21 (61.7%)	15 (51.7%)	0.422
Recipient BMI (kg/m^2)	24 (IQR: 21.0–32.0)	22 (IQR: 21.0–34.0)	0.29
MELD	16 (IQR: 14–19)	17 (IQR: 13–19)	0.531
Donor characteristics			
Donor age (years)	54 (IQR: 31–66)	56 (IQR: 28–64)	0.357
Donor time in ICU (hours)	78 (IQR: 25.0–137.0)	86 (IQR: 32.0–166.0)	0.092
Donor BMI (kg/m^2)	29 (IQR: 24.0–35.0)	32 (IQR: 25.0–38.0)	0.252
Noradrenaline dose >1000 ng/mL or 2 vasopressors (n, %)	13 (34.7%)	7 (41.1%)	0.231
Na (mmol/L)	148 (IQR: 134–155)	142 (IQR: 135–154)	0.152
AST (U/L)	44.0 (IQR: 24.0–79.0)	47.0 (IQR: 24.0–78.0)	0.82
ALT (U/L)	59.0 (IQR: 26.0–142)	61.0 (IQR: 32.0–91.5)	0.139
Macrosteatosis >40%	24 (70.6%)	23 (79.3%)	0.564
Perioperative parameters			
Cold ischemia time (hours)	5.2 (IQR: 4.4–8.0)	5.7 (IQR: 4.3–7.8)	0.29
Static cold storage time (hours)	7.2 (IQR: 4.8–8.3)	2.5 (IQR: 1.5–4.5)	**0.012**
Operation duration (min)	6.8 (IQR: 5.5–7.5)	6.3 (IQR: 4.8–8.3)	0.457
Secondary warm ischemia time (min)	40 (IQR: 30–45)	35 (IQR: 35–45)	0.28
Biliary ischemia time (min)	40 (IQR: 35–45)	40 (IQR: 35–50)	0.93
Blood loss (mL)	1400 (IQR: 1100–2500)	1100 (IQR: 1000–2500)	0.21
Reinfusion (mL)	300 (IQR: 100–450)	250 (IQR: 50–450)	0.62
FFP transfusion (doses)	6 (IQR: 3–8)	4 (IQR: 2–7)	0.42
Erythrocyte suspension transfusion (doses)	1 (IQR: 0–3)	1 (IQR: 0–2)	0.652
Immediate liver transplant outcomes			
Length of stay in ICU (days)	5 (IQR: 3–9)	3 (IQR: 2–5)	**0.042**
Length of stay in hospital (days)	21 (IQR: 17–35)	15 (IQR: 12–24)	**0.028**
Peak AST level (U/L)	1052 (IQR: 712–1842)	1943 (IQR: 1294–5214)	**0.002**
Peak ALT level (U/L)	1213 (IQR: 613–2032)	2318 (IQR: 1032–6219)	**<0.001**
EAD (n, %)	21 (61.8%)	12 (41.3%)	0.106
Non-specific surgical complications (n, %)	11 (32.3%)	5 (9.4%)	**0.01**
Arterial thrombosis (n, %)	3 (8.9%)	1 (3.4%)	0.383
CCI	27.6 (IQR: 0–100)	0 (IQR: 0–22.6)	**<0.001**
Retransplantation (n, %)	1 (2.9%)	0	1
Mortality (n, %)	2 (5.9%)	0	0.495

Note. BMI, body mass index; ICU, intensive care unit; Na, sodium; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FFP, fresh frozen plasma; EAD, early allograft dysfunction; CCI, comprehensive complication index.

on the preservation method. After graft delivery to the operating room, just before the beginning of machine perfusion, the first sample (1.1) was excised from the liver margin and fixed in formalin. At the same stage, a 2×2 cm fragment was excised from the liver and separately immersed in a cooled non-oxygenated preservative solution. Upon completion of machine perfusion preservation, the samples (1.2 and 1.3) were excised both from whole liver and from pre-cut fragments, which were under static cold storage conditions, and fixed in formalin. The sequence in which samples are taken for graft electron microscopy is presented in Fig. 3.

The immediate LTx outcomes depending on preservation method were analyzed by us in a comparative clinical study.

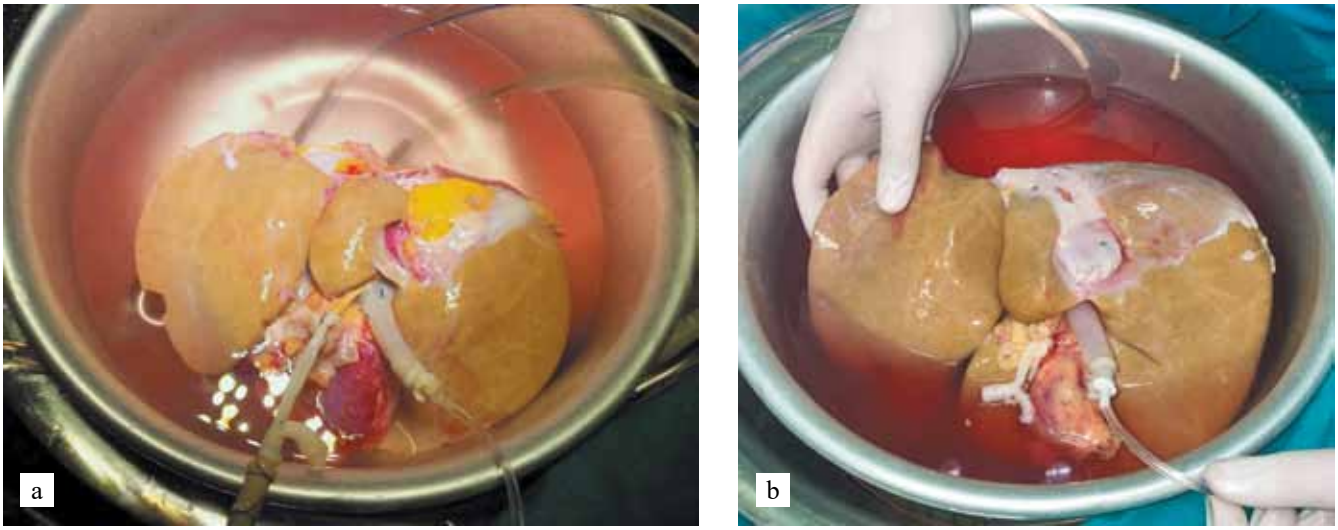

Fig. 1. Intraoperative photo: cannulation of the artery and portal vein of liver graft before the start of HOPE. a, dual perfusion of liver via the portal vein and hepatic artery; b, classic perfusion of liver via the portal vein

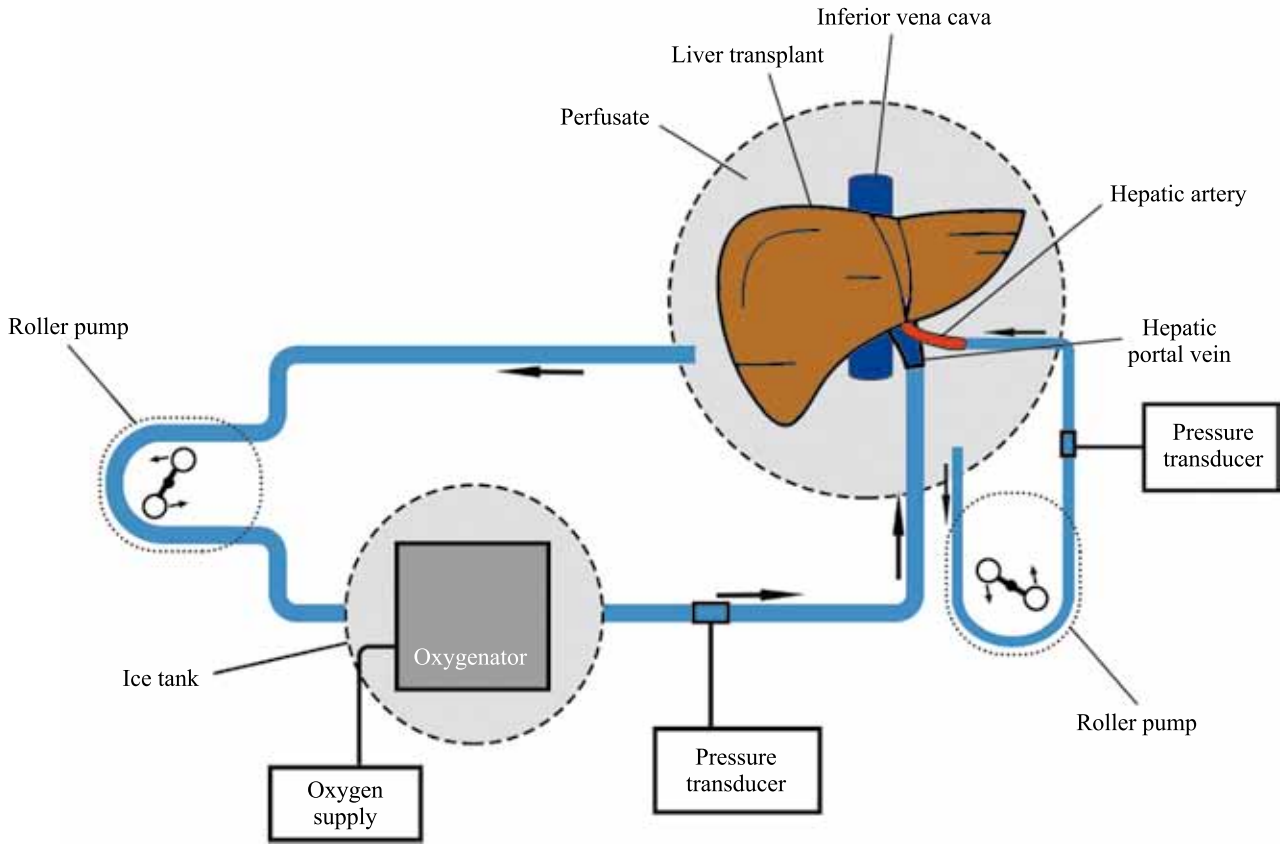

Fig. 2. Schematic representation of dual HOPE of the liver graft

Statistics

Statistical data processing and analysis were performed in the SPSS Statistics for Microsoft Windows 26 version (USA) program. Mann–Whitney U test was used to compare two groups of quantitative indicators due to the small sample size regardless of distribution. Categorical indicators were compared using Pearson's chi-squared test or Fisher's exact test. To determine the relationship between quantitative indicators, correlation analysis was performed with the determination of Spearman's rank correlation coefficient ρ and the closeness of the relationship using the Chaddock scale. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Comparative analysis of liver transplant outcomes depending on preservation method

The groups were found to have no statistically significant differences in terms of baseline donor and recipient characteristics ($p > 0.05$). The total cold storage time did not differ between the groups: 5.2 (IQR: 4.4–8.0) vs. 5.4 (IQR: 4.2–7.3), ($p = 0.32$). There were no statistically significant differences in terms of total surgical intervention time, secondary warm ischemia time and biliary ischemia time ($p > 0.05$). Intraoperative blood loss and the need for blood transfusion also did not differ ($p > 0.05$).

Peak AST and ALT levels in the first week after transplantation in group II (HOPE) were 1052 (IQR: 712–1842) U/L and 1213 (IQR: 613–2032) U/L. In the control group, these values were 1943 (IQR: 1294–5214) U/L and 2318 (IQR: 1032–6219) U/L, which were statistically significantly lower than in the main group ($p = 0.002$ and $p < 0.001$, respectively). At the same time, no statistically significant differences were found in EAD incidence ($p = 0.106$). However, it was lower in the machine perfusion preservation group: 41.3% (12/29) vs. 61.8% (21/34). EAD was irreversible in two group I cases, which was considered as PNF, and resulted in early postoperative mortality of both recipients. In one case, retransplantation was performed for hepatic artery thrombosis. In group II, there was no postoperative mortality, PNF, or retransplantation.

Early postoperative complications were assessed by calculating comprehensive complication index (CCI) at the time of discharge. Median CCI was 0 (IQR: 0–22.6) in the main group, and 27.6 (IQR: 0–100) in the control group; the differences were statistically significant ($p = 0.001$). Similarly, statistically significant differences were recorded in terms of the time the recipient spent in the ICU and the total length of stay in the hospital ($p = 0.042$ and $p = 0.028$) – these parameters were less in the machine perfusion preservation group. A comparative analysis of LTx outcomes between the groups is presented in Table 1.

Influence of laboratory perfusion parameters on clinical outcomes of liver transplantation

In group II (HOPE), we also examined the impact of perfusate laboratory markers (AST and ALT), determined at 30 minutes, on early postoperative transplant outcomes in group II (HOPE). Median perfusate AST level was 589 (IQR: 272–1712) U/L, and ALT level was 482 (IQR: 214–1513). In the first week following transplantation, these levels exhibited statistically significant direct correlations with peak levels of these in the recipient's blood. In particular, perfusate AST levels at 30 minutes of perfusion correlated strongly with peak AST and ALT levels ($\rho = 0.723$ and $\rho = 0.712$, $p < 0.001$ and $p < 0.001$). Perfusate ALT level also had statistically significant relationships with blood transaminases, although not as strongly correlated ($\rho = 0$, 0.662 and $\rho = 0.389$, $p < 0.001$ and $p = 0.04$). Perfusate AST and ALT levels had no significant associations with total bilirubin level and INR value on day 7 after transplantation ($p > 0.05$). Length of ICU stay and total length of stay in the hospital were also not associated with perfusate transaminases ($p > 0.05$). The results are presented in Table 2.

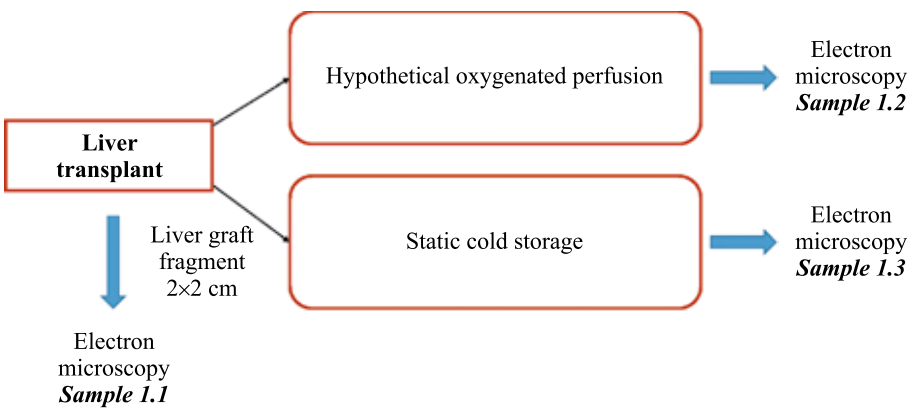

Fig. 3. Protocol for taking samples for liver graft electron microscopy

Morphological assessment of liver transplants depending on preservation method

Fig. 4, a shows an electron microscopy image of a hepatocyte fragment from sample 1.1 (liver before perfusion). Chromatin in the nucleus has a typical organization. The cytoplasm is filled with vesicles and mitochondria. The cristae in the granular endoplasmic reticulum are not dilated. The mitochondrial matrix is electronically dense, with few cristae. A similar picture was observed in sample 1.2 (liver after hypothermic oxygenated perfusion),

Table 2

Influence of laboratory perfusion parameters on immediate liver transplant outcomes

Indicators	Significance (p value)	Spearman's correlation coefficient ρ
AST level in the perfusate at 30 minutes of perfusion		
Peak AST level in the first week	**<0.001**	0.723
Peak ALT level in the first week	**<0.001**	0.712
INR on day 7	0.63	–
Total bilirubin on day 7	0.34	–
CCI	0.212	–
Length of stay in ICU	0.79	–
Length of stay in hospital	0.43	–
ALT level in the perfusate at 30 minutes of perfusion		
Peak AST level in the first week	**<0.001**	0.662
Peak ALT level in the first week	**0.04**	0.389
INR on day 7	0.74	–
Total bilirubin on day 7	0.82	–
CCI	0.65	–
Length of stay in ICU	0.29	–
Length of stay in hospital	0.72	

Note. AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; CCI, comprehensive complication index; ICU, intensive care unit.

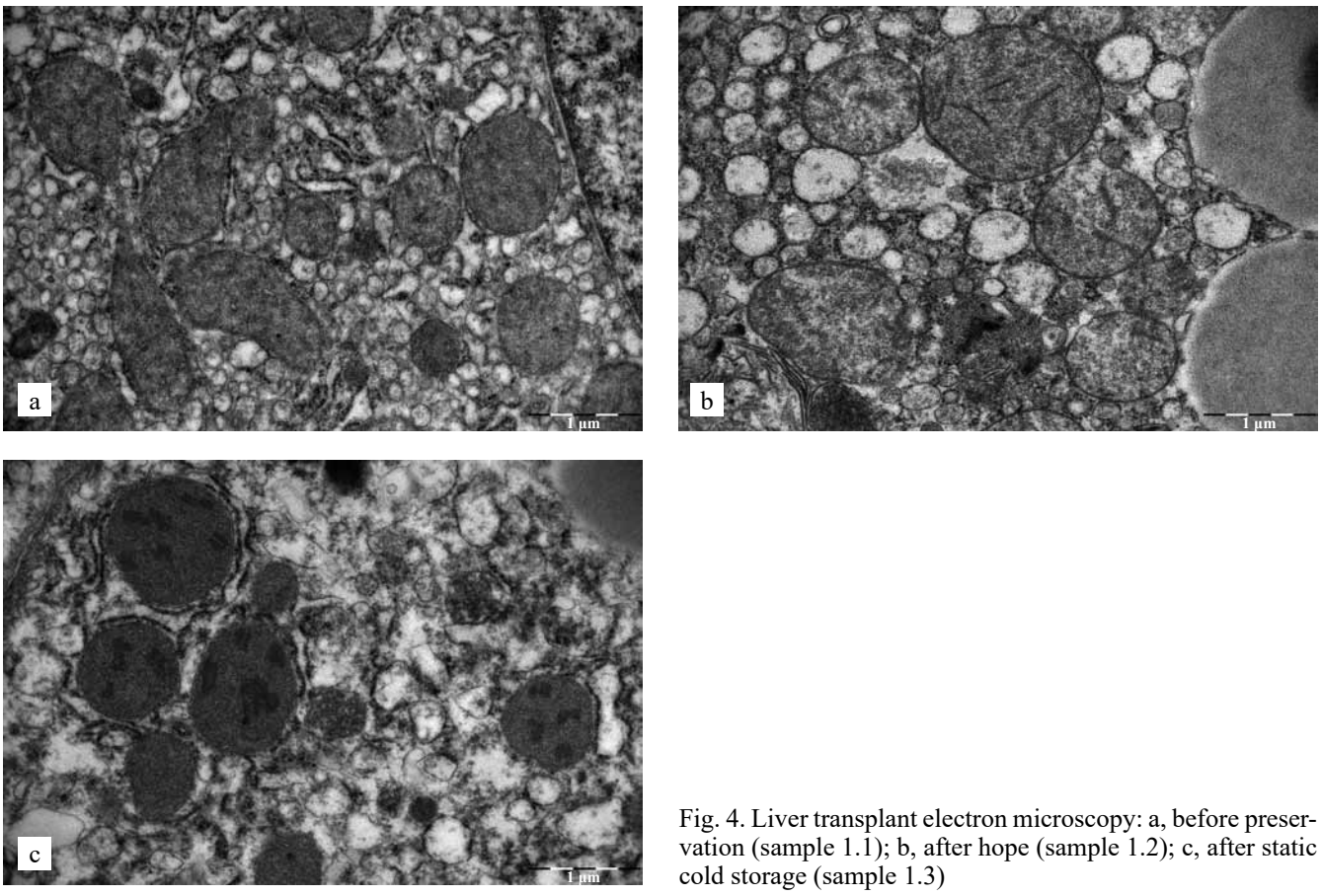

Fig. 4. Liver transplant electron microscopy: a, before preservation (sample 1.1); b, after hope (sample 1.2); c, after static cold storage (sample 1.3)

except for slight lucidity of the cytosol and swelling of the cristae in the granular endoplasmic reticulum. The ultrastructure of mitochondria is not altered (Fig. 4, b). On the contrary, during static liver preservation (sample 1.3), there were pronounced ultrastructural changes in the hepatocytes. The structure of the mitochondria underwent significant rearrangement, membrane stacks appeared and the granular endoplasmic reticulum swelled (Fig. 4, c).

DISCUSSION

The findings reported in this paper further support the association between LTx from ECDs and increased risk of EAD and its adverse effects. Thus, it is imperative to develop and implement technologies aimed at preventing IRI to the liver graft.

Machine perfusion preservation was introduced into the clinical practice of LTx just over 10 years ago, but many studies have already shown that it is superior to static cold storage. Guarrera et al. (2010) demonstrated that HOPE resulted in lower severity of reperfusion injury, lower incidence of EAD and shorter hospital stay [12]. Dutkowski et al. in 2014 published a successful experience of LTx from controlled non-heartbeating donors, in which HOPE had outcomes comparable to those after transplantation from a brain-dead donor [13]. In our study, the use of HOPE was also associated with better liver transplant outcomes in the early postoperative period. Compared to static storage, the degree of ischemic injury to the liver after perfusion was less significant, which was clearly confirmed by electron microscopy. The intensity of graft reperfusion injury, determined by peak transaminase levels during the first week, was statistically significantly lower in the machine perfusion preservation group than in the static preservation group ($p < 0.05$). We found no statistically significant reduction in EAD risk ($p = 0.106$). However, we attribute this to the small sample size. Meanwhile, CCI decreased significantly ($p = 0.001$), which characterizes the prevalence of postoperative complications, duration of recipient's stay in ICU ($p = 0.042$) and inpatient treatment ($p = 0.028$).

Apart from mitigating harm to the liver transplant during preservation, another advantage of HOPE was the ability to conduct further assessment of organ quality and suitability for transplantation. Thus, we found that perfusate transaminase levels at 30 minutes were directly correlated with those in the recipient's blood after transplantation ($p < 0.05$).

However, the predictive value of these indicators is limited as they did not show any correlation with immediate transplant outcomes. Nevertheless, we believe that it is advisable to determine the levels because the transplant team might decide not to proceed with transplantation if there are abnormally high AST and ALT levels in the perfusate since the risk of death is too high. Four such cases have led us to ultimately decide against transplantation due to abnormally high AST levels (>6000 U/L) in the effluent determined at 30 minutes after perfusion.

The results are consistent with global reports. In the aforementioned works by Guarrera and Dutkowski, perfusate transaminase levels likewise exhibited a statistically significant correlation with those in the recipient's blood during reperfusion, but they had no bearing on the recipient's prognosis [12–14]. Currently, many authors are searching for more accurate markers that can be determined during perfusion preservation for organ assessment. In particular, the determination of mitochondrial injury markers in the perfusion solution – such as FMN – has demonstrated high efficiency in assessing organ compatibility in several studies; nevertheless, further research is needed to confirm and validate this approach's wider application [14].

Even though machine perfusion preservation in LTx from suboptimal donors has been shown to be highly efficient, there are still a lot of unresolved technical issues around its use. For example, it is not completely known whether additional arterial perfusion of the graft (dual HOPE/DHOPE) or perfusion via the portal vein (classic HOPE) is adequate. DHOPE proponents contend that because bile ducts receive their supply exclusively from the hepatic artery, as opposed to hepatocytes, this approach may enable more effective perfusion of the biliary tree. Since post-transplant cholangiopathy is one of the most significant problems in LTx from marginal donors (in particular, non-heartbeating donors), prevention of IRI of the hepatic biliary system is very relevant. On the other hand, proponents of classic perfusion believe that the arterial bed can be adequately filled with perfusate due to retrograde current, and additional manipulations with the hepatic artery may lead to its injury and fatal complications.

To date, there are no clinical studies demonstrating the superiority of one method over the other, apart from an experimental work by de Vries et al. (2021), which demonstrated a 2-fold decrease in peak ALT levels in the perfusate ($p = 0.045$) and a lower peak lactate dehydrogenase in the bile ($p = 0.04$) of livers preserved by DHOPE in comparison with classic HOPE [15]. At the same time, none of the groups showed any microscopic sign of arterial injury. Although further clinical validation is still needed, we believe that extra arterial perfusion of the liver still offers a slightly higher potential efficacy than the classical approach. We believe that the danger of injury to the hepatic artery during the procedure is actually mitigated by the precise surgical technique used to deal with the hepatic artery and careful regulation of flow and pressure in the arterial perfusion system.

Thus, ex situ HOPE is a safe and effective liver transplant preservation technique. Its application in LTx from ECDs enables a more thorough evaluation of an organ's suitability for transplantation while also lessening the severity of IRI. This technique can improve LTx outcomes

in the postoperative period, while also safely increasing the availability of transplant care using suboptimal donors.

The authors declare no conflict of interest.

REFERENCES

1. Eurotransplant Annual Report 2022. [Internet] Available from: https://www.eurotransplant.org/statistics/annual-report/.
2. *Moysyuk YaG, Poptsov VN, Sushkov AI, Moysyuk LYa, Malinovskaya YuO, Belskikh LV*. Early liver allograft dysfunction: risk factors, clinical course and outcomes. *Transplantologiya. The Russian Journal of Transplantation*. 2016; (2): 16–28. [In Russ, English abstract].
3. *Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J et al.* Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl*. 2010; 16 (8): 943–949. doi: 10.1002/lt.22091.
4. *Lee DD, Croome KP, Shalev JA, Musto KR, Sharma M, Keaveny AP et al.* Early allograft dysfunction after liver transplantation: an intermediate outcome measure for targeted improvements. *Ann Hepatol.* 2016; 15 (1): 53–60. doi: 10.5604/16652681.1184212.
5. *Hartog H, Hann A, Perera MTPR.* Primary Nonfunction of the Liver Allograft. *Transplantation.* 2022; 106 (1): 117–128. doi: 10.1097/TP.0000000000003682.
6. *Fedoruk DA, Kirkovsky LV, Sadovsky DN, Petrenko KI, Lebed' OA, Fedoruk AM et al.* Influence of hypothermic oxygenated machine perfusion on the degree of ischemic damage of ecd liver grafts. *Military medicine.* 2020; (2): 68–75. [In Russ, English abstract].
7. *Czigany Z, Pratschke J, Froněk J, Guba M, Schöning W, Raptis DA et al.* Hypothermic Oxygenated Machine Perfusion Reduces Early Allograft Injury and Improves Post-transplant Outcomes in Extended Criteria Donation Liver Transplantation From Donation After Brain Death: Results From a Multicenter Randomized Controlled Trial (HOPE ECD-DBD). *Ann Surg.* 2021; 274 (5): 705–712. doi: 10.1097/SLA.0000000000005110.
8. *Mugaanyi J, Dai L, Lu C, Mao S, Huang J, Lu C.* A Meta-Analysis and Systematic Review of Normothermic and Hypothermic Machine Perfusion in Liver Transplantation. *J Clin Med.* 2022; 12 (1): 235. doi: 10.3390/jcm12010235.
9. *Shabunin AV, Minina MG, Drozdov PA, Nesterenko IV, Makeev DA, Zhuravel OS et al.* Early experiments with hypothermic oxygenated machine perfusion of kidney grafts from extended criteria donors. *Russian Journal of Transplantology and Artificial Organs*. 2022; 24 (1): 143–150. doi: 10.15825/1995-1191-2022-1-143-150.
10. *Shabunin AV, Minina MG, Drozdov PA, Sevostianov VM, Nesterenko IV, Makeev DA et al.* Asystole kidney donation using automated chest compression system and hypothermic oxygenated machine perfusion (first experience in the Russian Federation). *Russian Journal of Transplantology and Artificial Organs*. 2022; 24 (2): 102–107. doi: 10.15825/1995-1191-2022-2-102-107.
11. *Shabunin AV, Minina MG, Drozdov PA, Miloserdov IA, Saydulaev DA, Sevostyanov VM et al.* Complex use of perfusion techniques in kidney transplantation from a donor with out-of-hospital cardiac arrest (clinical case). *Russian Journal of Transplantology and Artificial Organs*. 2023; 25 (3): 113–121. doi: 10.15825/1995-1191-2023-3-113-121.
12. *Guarrera JV, Henry SD, Samstein B, Odeh-Ramadan R, Kinkhabwala M, Goldstein MJ et al.* Hypothermic machine preservation in human liver transplantation: the first clinical series. *Am J Transplant*. 2010; 10 (2): 372–381. doi: 10.1111/j.1600-6143.2009.02932.x.
13. *Dutkowski P, Schlegel A, de Oliveira M, Mullhaupt B, Neff F, Clavien PA.* HOPE for human liver grafts obtained from donors after cardiac death. *J Hepatol.* 2014; 60: 765–772. doi: 10.1016/j.jhep.2013.11.023.
14. *Muller X, Schlegel A, Kron P, Eshmuminov D, Würdinger M, Meierhofer D et al.* Novel Real-time Prediction of Liver Graft Function During Hypothermic Oxygenated Machine Perfusion Before Liver Transplantation. *Ann Surg*. 2019; 270 (5): 783–790. doi: 10.1097/sla.0000000000003513.
15. *De Vries Y, Brüggenwirth IMA, Karangwa SA, von Meijenfeldt FA, van Leeuwen OB, Burlage LC et al.* Dual Versus Single Oxygenated Hypothermic Machine Perfusion of Porcine Livers: Impact on Hepatobiliary and Endothelial Cell Injury. *Transplant Direct.* 2021; 7 (9): e741. doi: 10.1097/TXD.0000000000001184.

The article was submitted to the journal on 21.01.2024