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The impact of desflurane and sevoflurane on the intraoperative and early postoperative period in liver transplantation

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Abstract

Background. *A pressing issue is the choice of an anesthetic agent for liver transplantation. The mechanism of the organ-protective properties of desflurane and sevoflurane is not fully understood. It is important to understand the effects of desflurane and sevoflurane on the severity of ischemia-reperfusion injury of the liver graft*

Aim. *To study the effect of desflurane and sevoflurane on the intraoperative and early postoperative period in liver transplantation.*

Material and methods. *The study included 47 patients with liver cirrhosis of various etiologies who underwent cadaveric liver transplantation between February and December 2020. The groups compared in the study included 24 patients who received desflurane and 23 patients who received sevoflurane.*

Results. *There were no statistically significant differences in the effect of desflurane and sevoflurane on hemodynamic parameters, on the need for vasopressor drugs. Episodes of bradycardia and cardiac arrhythmias were significantly more frequent when using sevoflurane. Patients were*

extubated significantly faster after surgery in the desflurane group. In the early postoperative period, desflurane and sevoflurane did not adversely affect significantly the liver graft function and the degree of its ischemia-reperfusion injury. The groups appeared comparable in rates of using the renal replacement therapy, the incidence of the graft dysfunction development in the postoperative period, and the surgery outcomes.

Conclusions. *The use of modern inhalation anesthetics desflurane and sevoflurane to maintain anesthesia during liver transplantation does not adversely affect the course of the intraoperative and early postoperative period.*

Keywords: inhalation anesthetics, desflurane, sevoflurane, liver transplantation

Conflict of interests Authors declare no conflict of interest

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ABB, acid-base balance

ALT, alanine aminotransferase

APTT, activated partial thromboplastin time

AST, aspartate aminotransferase

BMI, body mass index

BP, blood pressure

CETA, combined endotracheal anesthesia

CVP, central venous pressure

ECG, electrocardiogram

FG, fresh gas

HR, heart rate

IAA, inhalational anesthetic agent

ICU, Intensive Care Unit

INR, International Normalized Ratio

MAC, minimum alveolar concentration

MAP, mean arterial pressure

MLV, mechanical lung ventilation

RRT, renal replacement therapy

VC, Volume Control, volume controlled mechanical ventilation mode

Introduction

The role of today anesthetic support is not only to solve the problem of taking away pain sensitivity and ensuring patient safety during surgical interventions, but also to solve a number of important additional tasks that can affect the treatment outcome [1, 2].

Therefore, assessing the properties of anesthetic agents and their impact on organ systems has always been a top priority for an anesthesiologist when performing anesthesia in a particular area of surgery. This is especially true for those interventions that are performed in patients with severe renal and hepatic dysfunctions, for example, in transplantation of these organs.

Numerous studies have identified the third-generation inhalational anesthetics, sevoflurane and desflurane, as the drugs of choice in anesthesiology. They are recommended for wide clinical use. They are highly efficient, manageable, and safe.

Instead of being organotoxic, modern inhaled anesthesia products are considered to have organ-protective properties, such as myocardial preconditioning, bronchodilation, and neuroprotection.

The absence of biotransformation and the elimination unchanged, as well as minimal side effects on organs and systems, are important properties of the "ideal" anesthetic. Since there is currently no "perfect" anesthetic, the risk of side effects should be considered by the anesthesiologist in order to ensure patient safety.

The process of biotransformation of an anesthetic agent is important for the clinician because it is closely related to liver and kidney functions. There are different opinions about negative effects of inhalational anesthetics on the liver function. Acute liver necrosis is a process that is initiated by peroxidation of a halogen-containing anesthetic with the formation of trifluoroacetate. The metabolism of sevoflurane excludes the formation of trifluoroacetate; and desflurane, although it forms trifluoroacetate during biodegradation, is subjected to biotransformation to a small extent. The likelihood to liver damage is found in desflurane with an incidence of less than 0.02% [3-5].

Although the level of trifluoroacetate in desflurane is 1000 times lower than that of halothane, and the low hepatotoxicity of desflurane has been clinically confirmed, an analysis of literature data from different countries for 1999-2010 found 5 cases when toxic hepatitis resulting from anesthesia with desflurane led to a fatal outcome [6].

When performing anesthetic support, the liver functional status changes under the impact of the anesthesia components, but, to even a greater extent, of the surgery per se, the ventilation mode, infusion, etc. As for the intraoperative effects on the liver, the following factors have been distinguished: the operation factors (bleeding, mechanical damage, hypercatecholaminemia); factors associated with blood transfusion therapy, ventilation mode and its effect on the oxygen and carbon dioxide homeostasis that depend on ventilation; the effect of anesthetics and other medications used during surgery and anesthesia.

For example, H. Fukuda et al. [7] studied the liver functional state by determining the plasma concentration of hepatocyte growth factor and making standard laboratory tests before and after intra-abdominal operations performed under sevoflurane anesthesia in patients with a normal liver function and liver dysfunction. Standard laboratory tests did not reveal any abnormalities in both groups, while hepatocyte growth factor was statistically significantly increased in the groups of patients with liver dysfunction. This study demonstrated liver damaging during anesthesia with sevoflurane in case of its initial pathology, and the hepatocyte growth factor is a more sensitive marker of this process. Later, in their study, S. M. Al Ghanem et al. [8] found an increase in total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in obese patients during anesthesia with sevoflurane, and total bilirubin remained elevated for 7 days of the postoperative period.

It is obvious that the status of patients undergoing liver transplantation surgery is usually characterized by an extremely severe liver dysfunction and, as a result, impaired functions of other organ systems. Therefore, the following must be taken into detailed account:

- The selection of the optimal anesthetic and its dosage;
- The impact of risk factors that occur during surgery (blood loss, hypothermia, surgery specific features, etc.),
- The need to optimize the fluid therapy and blood transfusion,
- The use of the necessary additional anesthesiology monitoring.

Thus, the survey on the effects that inhalational anesthetics cause is still open and controversial [9, 10]. The inhalational anesthetic desflurane is increasingly used in anesthetic practice [11]. According to a number of studies [12], desflurane shows a more pronounced organ-protective effect during kidney transplantation compared to isoflurane and sevoflurane.

Meantime, the choice of an inhalational anesthetic agent during a liver transplant surgery is still debatable. The mechanism of organ-protective action of desflurane and sevoflurane is also unclear. It is also important to understand the effect of inhalational anesthetics on the severity of ischemia-reperfusion syndrome in organ transplantation.

The aim of this study was to investigate the effect of inhalational anesthetics, desflurane and sevoflurane, on the intraoperative and early postoperative period in liver transplantation.

Material and methods

A prospective single-center randomized study was conducted at the base of the Liver Transplantation Center of N.V. Sklifosovsky Research Institute of the Moscow Healthcare Department from February 2020 to December 2020. The study included 47 patients with liver cirrhosis of various etiologies, of class B and class C severity by Child–Pugh classification. All patients underwent successful orthotopic liver transplantation from a postmortem donor. Patients were randomly assigned to two groups for comparison depending on the intraoperative inhalational anesthetic agent (IAA) used: group I included 24 patients for whom desflurane was used as IAA, and group II included 23 patients for whom sevoflurane was used. The random distribution method was used.

The study inclusion criteria:

1. Orthotopic liver transplantation from a postmortem donor under combined endotracheal anesthesia (CETA) in patients with liver cirrhosis of various etiologies, Child-Pugh severity class B or;
2. Patients aged from 18 to 70 years.

Exclusion criteria:

1. Combined kidney and liver transplantation;
2. Hepatic coma;

3. Related liver transplantation;
4. Terminal patient's condition;
5. MELD score over 30;
6. Fulminant liver failure;
7. Expanded criteria donor.

The patients in the groups were comparable in age, height, and body weight. There was a slight predominance of men in number in the desflurane group compared to the sevoflurane group (p=0.05) (Table 1).

Table 1. Characteristics of groups by patient gender, age and anthropometric data

Characteristics	Desflurane group n=24 (Me (1;3))	Sevoflurane group n=23 (Me (1;3))	p
Age (years)	52 (37;61)	57.0 (43.5;64)	0.146
Gender: male female	 20 3	 11 13	0.05
Height (cm)	175 (168;183)	170 (164;179)	0.134
Weight (kg)	80 (71;90)	74 (65;88)	0.358
BMI	25 (23.4;29.1)	25.7 (22.2;28.2)	0.696

According to the Child-Pugh classification of liver cirrhosis severity, the desflurane group included 73.9% of Class C patients and 26.1% of Class B patients; the sevolurane group included 75% of Class C patients and 25% of Class B patients. No statistically significant differences were found (p>0.05).

Characteristics of organ donors

For preoperative assessment of the donor organ quality, the age of the donor, the length of stay in the intensive care unit (ICU), diurnal diuresis, azotemia and serum liver enzymes were taken into account. The graft cold ischemia time was also monitored.

According to the Mann-Whitney test, there was no statistically significant differences between the groups in the characteristics of the donor organ. The results are presented in Table 2.

Table 2. Characteristics of donors and donor organs

Characteristics	Desflurane group n=24 (Me (1;3))	Sevoflurane group n=23 (Me (1;3))	p
Donor age, years	51.5 (33.5;57.5)	51 (45; 61)	0.322
Number of days in the ICU	2 (1;3.5)	3 (1; 4)	0.773
Donor diuresis per 24 hours, mL	3950 (3075;5000)	4000 (3150; 5300)	0.765
Urea, mmol/L	5.45 (4.4;9.5)	5.9 (4;8.4)	0.823
Creatinine, μmol/L	102.35 (69.3;118.85)	77.1 (67.5;103)	0.197
AST, U/L	42.5 (24;55.55)	39 (20.9;58)	0.61
ALT, U/L	30.75 (22.2;69.5)	28 (22;45)	0.338
Donor organ cold ischemia time, min	362.5 (232;392.5)	367 (315;403)	0.881

Note: ALT: alanine aminotransferase; AST: aspartate aminotransferase

Tactics of providing anesthesia

Anesthesia induction was provided with propofol 10 mg/mL, 20 ml, at a dose of 2-2.5 mg/kg in combination with fentanyl 50 mcg/mL, 2 ml, 3-5 mcg/kg against the background of muscle relaxation with cisatracurium bezilate 150 mcg/kg. After the onset of muscle relaxation, the tracheal intubation was performed, mechanical lung ventilation (MLV) was started, and the IAA supply was switched on. Anesthesia was performed using a Dräger Primus Anesthesia Workstation with Volume Control (VC) ventilation along a semi-closed circuit.

Inhalational anesthetics were administered in the following concentrations: 12.0 vol.% (fresh gas [FG] flow in the circuit of 2 L/min) for desflurane, 4.0 vol.% (FG flow in the circuit of 4 L/min) for sevoflurane. After the minimum alveolar concentration (MAC) of 1.0 vol% had been reached, the IAA was supplied according to the principle

of minimal flow anesthesia (the FG flow in the circuit was no more than 0.5 L/min) in the desflurane group, the FG flow was 2 L/min in the sevoflurane group.

After tracheal intubation and initiation of inhalation anesthesia, all patients underwent sequential puncture and catheterization of the right internal jugular vein with a two- or three-lumen high-flow catheter, those of the right subclavian vein with a single-lumen catheter for infusion-transfusion therapy, renal replacement therapy (RRT) in the post-transplant period, if necessary, for venous blood sampling to study the acid-base balance, blood gases. For the purpose of blood pressure (BP) invasive monitoring, after receiving a positive Allen test, a sequential puncture and catheterization of the right radial artery was performed. A nasogastric tube was inserted into the stomach. The bladder catheterization was performed to control hourly diuresis.

Electrocardiogram (ECG), the heart rate (HR), pulse oximetry, blood pressure, including mean arterial pressure (MAP), central venous pressure (CVP), were monitored by indirect and direct methods. For statistical analysis, blood pressure and heart rate were recorded at 4 time-points: at the time of the surgery start, at 10 minutes before reperfusion, 5 minutes after reperfusion, and at the time of the surgery completion.

Episodes of arrhythmia, bradycardia (HR<50 beats/min), tachycardia (HR>90 beats/min), hypotension (SBP<80 mm Hg), hypertension (SBP>150 mm Hg), and other complications were also taken into account.

After the surgery was completed, the patient was transferred to the Intensive Care Unit, where, during the patient recovery process, doctors recorded the time interval during which the patient opened his eyes, squeezed a hand and was extubated. Vital functions, hourly diuresis, RRT

sessions, complications, and outcomes were also assessed in the postoperative period.

Surgical complications were not considered.

Statistical analysis

Parametric and nonparametric statistical methods were used to calculate the following values: mean, standard deviation, median, quartile range. The variance analysis of two groups with independent distribution (Kruskal-Wallis test) was performed, and the χ-square was calculated. The Wilcoxon test was used to compare the results of data before and after IAA administration. P values of <0.05 were considered statistically significant. The statistical analysis was performed using Statistica 12.0 software package.

Results

Intraoperative period

The groups were comparable in the requirements in muscle relaxants and fentanyl in the intraoperative period and did not differ statistically significant (Table 3).

Table 3. The requirement in muscle relaxants and fentanyl

Drug	Desflurane group n=24 (Me (1;3))	Sevoflurane group n=23 (Me (1;3))	p
Muscle relaxant, mg	70 (60;70)	70 (70;90)	0.267
Fentanyl, mg	1.05 (1;1.45)	1.2 (1;1.3)	0.591

No differences between the groups were recorded in the dynamics of blood pressure and heart rate at 4 time-points. Intraoperative

hypotension occurred in 33.3% of cases in the desflurane group and in 43.5% of cases in the sevoflurane group (Figure).

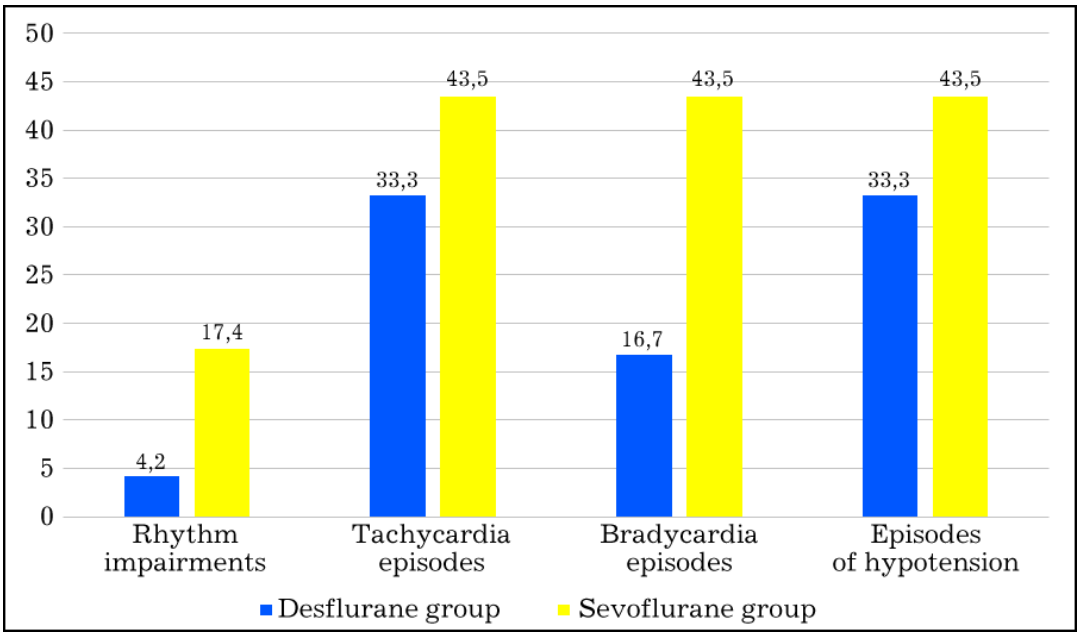

Figure. Negative impact on hemodynamics (in %)

Intraoperative tachycardia occurred in 33.3% of patients in the desflurane group and 43.5% in the sevoflurane group, bradycardia occurred in 16.7% of patients in the desflurane group and 43.5% of patients in the sevoflurane group (Figure). In patients in the sevoflurane group, there were statistically significant ($p<0.05$) heart rhythm disturbances: in 17.4% of cases versus 4.2% in the desflurane group.

One patient (4.2%) from the desflurane group showed signs of myocardial ischemia (tall T waves V3-V5) after 4 minutes of the venous reperfusion stage.

The need to use vasopressors for hemodynamics stabilization at the beginning of surgery occurred in 3 cases (12.5%) among the patients of the desflurane group, and in 8 (34.8%) patients in the sevoflurane group. At surgery completion, this was necessary in 20 patients (83%) in the desflurane group and in all 23 patients (100%) in the sevoflurane group.

To maintain hemodynamics, we used norepinephrine and dopamine. A combination of these drugs was administered, as a rule. In several patients, vasopressor support was provided in the form of monotherapy with either norepinephrine or dopamine, depending on the particular situation. We should note that one patient in the sevoflurane group was administered epinephrine in addition to norepinephrine and dopamine from the moment of venous reperfusion to the surgery completion.

The analysis of the doses of vasopressor support drugs at the start of surgery and at surgery completion showed no statistically significant difference between the desflurane and sevoflurane groups (Table 4).

Table 4. The requirement in vasopressors

Vasopressor	Desflurane group n=24 (Me (1;3))		Sevoflurane group n=23 (Me (1;3))		p	
	Surgery start	Surgery completion	Surgery start	Surgery completion	Surgery start	Surgery completion
Dopamine, μg/kg/min	0 (0;0)	3.25 (0;6)	0 (0;1.4)	4 (2.05;5)	0.265	0.828
Norepinephrine, μg/kg/min	0 (0;0)	90 (15;275)	0 (0;10)	300 (100;340)	0.459	0.200

We should note that there were no statistically significant differences between the groups in surgery duration, in the time of the anhepatic period and the volume of intraoperative blood loss.

The question of early extubation after liver transplantation is always open. The severity of the baseline condition of patients with end-stage liver cirrhosis, as a rule, does not allow the patient extubation in the operating room, especially after long surgery. On surgery completion, all patients on prolonged mechanical ventilation were transferred to the Intensive Care Unit where, if no contraindications, they were extubated

on the recovery of consciousness, adequate muscle tone, and spontaneous breathing.

We assessed time from the moment of anesthetic shutoff till extubation in the groups of patients. There was a statistically significant difference between the groups. In the desflurane group, the patients were extubated significantly sooner than in the sevoflurane group (Table 5).

Table 5. The interval from the moment of the inhalation anesthetic shut off till extubation

Procedure	Desflurane group n=24 (Me (1;3))	Sevoflurane group n=23 (Me (1;3))	p
Extubation, min	75 (60;180)	125 (120;300)	0.016

Early postoperative period

The impact of IAA on the liver graft function and the severity of ischemia-reperfusion injury in the early postoperative period were assessed by testing the levels of serum liver enzymes bilirubinemia at days 2, 3, and 5, and the dynamics of blood coagulation parameters (international normalized ratio [INR] and activated partial thromboplastin time [APTT]) (Table 6).

Table 6. Characteristics of the graft function in the early postoperative period

Parameter	Desflurane group n=24 (Me (1;3))			Sevoflurane group n=23 (Me (1;3))			p		
	Day 2	Day 3	Day 5	Day 2	Day 3	Day 5	Day 2	Day 3	Day 5
ALT, U/L	547.37 (418.9;729)	360.15 (258.2;455.8)	238 (171.3;459)	636 (400;1092)	424 (290;737)	296.52 (163.2;981.89)	0.388	0.221	0.704

AST, U/L	566.8 (319.9;947.5)	158.12 (115.8;309)	107.8 (85.1;178)	615 (378;1568)	240.32 (109.5;401)	88 (50; 19)	0.273	0.475	0.118
Bilirubin, μmol/L	37.135 (20;71.68)	19.335 (13.78;55.275)	25.365 (17.5;46.18)	30 (21.83;61.55)	29.4 (12.46;48.03)	23.535 (13.32;50.56)	0.594	0.823	0.549
INR	1.68 (155;1.91)	1.225 (1.17;1.4)	1.185 (1.095;1.32)	1.65 (1.42;2.08)	1.19 (1.07;1.4)	1.15 (1.085;1.27)	0.624	0.594	0.621
APTT, sec	32 (29.4;37.8)	28.35 (26.15;33.65)	27.3 (26.35;32.3)	35.3 (27.6;40.8)	26.8 (23.8;33.9)	25.65 (21.5;29.75)	0.886	0.523	0.265

Analysis of transaminase levels (ALT, AST) showed no statistically significant difference in these data between the patients in the desflurane and sevoflurane group. Similarly, there was no statistically significant increase in bilirubinemia in the groups on days 2, 3, and 5 after liver transplantation. The dynamics of blood coagulation parameters (INR and APTT) in patients in the desflurane and sevoflurane groups showed no statistically significant differences, either (Table 6).

Early graft dysfunction is a multifactorial syndrome that is characterized by laboratory parameter abnormalities during the first postoperative week and is determined by varied severity of ischemia-reperfusion injury to the graft. Within 7 days after liver transplantation, the patients were evaluated for a graft dysfunction in accordance with the criteria proposed by K. Oldhoff et al.: the blood level of bilirubin of more than or equal to 10 mg/mL, INR of more than or equal to 1.6, blood levels of aminotransferases (ALT, AST) of more than or equal to 2000 IU/L [13]. According to these criteria, the graft dysfunction was identified in 2 patients (8.4%) of desflurane group and in 4 patients (17.4%) in sevoflurane group.

RRT sessions were required to 3 patients (12.5%) from the desflurane group and 2 patients (8.7%) from the sevoflurane group (Table 7).

Table 7. Complications of the postoperative period

Complication	Desflurane group, n=24	Sevoflurane group, n=23
Graft dysfunction, %	2 (8.40)	4 (17.4)
RRT in the postoperative period, %	3 (12.5)	2 (8.7)

The surgery result were favorable in patients of both groups: the patients were discharged having a satisfactory liver graft function, with the exception of one (4.3%) fatal outcome (4.3%) in the sevoflurane group (Table 8).

Table 8. Outcomes of liver transplantation

Characteristic	Desflurane group, n=24	Sevoflurane group, n=23
Discharged from hospital having satisfactory graft function, %	100	95.7
Death, %	0	4.3

Discussion

Early liver dysfunction and anesthesia using an IAA, cumulatively, may affect the postoperative course [8]. Probably, a special place in surgical practice belongs to interventions when a patient with end-stage cirrhosis and a severe liver dysfunction is transplanted with a cadaveric organ which itself is exposed to many negative factors (clinical status of the donor, cold ischemia, warm ischemia, possible blood loss and hemodynamic disorders, etc.). This is the reason for special attention to the choice of IAA in liver transplantation.

In our study, the clinical status of liver donors and the time of cold ischemia of the graft did not differ statistically significantly. Recipients

who underwent liver transplantation under anesthesia with desflurane and sevoflurane were comparable in gender, age, anthropometric data, and severity of liver cirrhosis as assessed by the Child-Pugh classification.

The analysis showed that the need for muscle relaxants and opioids during anesthesia did not significantly differ between the patient groups of desflurane and sevofluran use. IAAs had different effects on the heart rate and cardiac rhythm during surgery: cardiac arrhythmias and episodes of bradycardia were statistically significantly more common when using sevoflurane. However, the number of patients with intraoperative tachycardia and hypotension did not differ statistically significantly by group. In one patient from the desflurane group, tall T waves in V3-V5 were recorded on the ECG monitor at the stage of venous reperfusion, which was regarded as myocardial ischemia.

Throughout the entire surgery, the patients in both groups needed vasopressor support to be used for hemodynamics stabilization. Meanwhile, the doses of vasopressors (norepinephrine, dopamine) at the time of the surgery start and surgery completion were comparable in the groups. Only one patient in the sevoflurane group required additional epinephrine administration from the moment of venous reperfusion to surgery completion.

It should be emphasized that our results were somewhat different from the results of a recent study conducted in patients with related liver transplantation. The authors compared patient groups with similar IAAs (either sevoflurane or desflurane) used and found a greater need for epinephrine use after restoration of venous blood flow in the graft in the desflurane group (19.4% vs. 45.2%, p=0.030).

The authors considered this fact as a manifestation of the reperfusion syndrome being more pronounced when using desflurane. At

the same time, the duration of treatment in the Intensive Care Unit and in hospital did not differ between the groups [14].

Our results in liver transplantation from a postmortem donor showed no statistically significant difference in the manifestations of reperfusion syndrome between the study groups. In addition, at surgery completion, the quickness of the recovery of consciousness, adequate muscle tone, and independent breathing depended on the IAA used. In the desflurane group, patients were extubated significantly sooner than in the sevoflurane group.

The impact of desflurane and sevoflurane on the graft function and the severity of ischemia-reperfusion injury in the early postoperative period did not differ statistically significantly. The need for RRT in the postoperative period was also comparable between the groups. It is worthwhile to note the study which compared the impacts of desflurane and isoflurane on the postoperative functioning of the liver and kidneys, as well as the impact of anesthetics on hemostasis in living related donors who underwent right-sided hemihepatectomy. The authors concluded that when using desflurane, a significantly lower increase in cytolysis enzymes is recorded in the early postoperative period, and the INR remains closer to the normal level at equivalent doses of an anesthetic agent in 1 MAC [15].

Conclusion

All patients were discharged after surgery with a satisfactory graft function. One fatality was reported in the sevoflurane group. Both inhalational anesthetics, desflurane and sevoflurane, have a certain impact on hemodynamics during liver transplantation, which requires a statistically significant administration of vasopressors.

The advantage of desflurane includes a statistically significantly sooner awakening and extubation of patients after the intervention.

The use of desflurane or sevoflurane does not negatively affect the liver graft function and the severity of its ischemia-reperfusion injury in the early postoperative period.

Conclusion

The use of current inhalational anesthetics desflurane and sevoflurane to maintain anesthesia during liver transplantation does not negatively affect the course of the intraoperative and early postoperative period.

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