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Comparison of the effects of inhalation anesthetics in the intra- and postoperative periods during kidney transplantation

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Background. *Every year the number of patients with chronic renal failure is steadily increasing. Allogeneic kidney transplantation from a post-mortem donor is a radical method to cope with chronic renal failure, improving the quality and life expectancy of patients. Currently available inhalation anesthetics make it easy to control the depth of anesthesia; they are excreted by the lungs unchanged, providing a quick emergence from anesthesia and easy waking up of the patient. An "ideal" inhalation anesthetic used for kidney transplantation should have a minimal amount of adverse effects.*

The aim *was to compare the efficacy of inhaled anesthetics used for allogeneic kidney transplantation from a posthumous donor.*

Material and methods. *A randomized, prospective, single-center study included 62 patients with end-stage chronic renal failure. The subjects were divided into three groups depending on the type of the inhalation anesthetic used. The first group included patients who underwent low-flow inhalation anesthesia with desflurane, the second and third groups were comparator groups where patients received sevoflurane or isoflurane, respectively, as an inhalation anesthetic. When assessing hemodynamic parameters, most episodes of hemodynamic instability were seen in the isoflurane group; the most stable statistically significant values were observed in the sevoflurane group, and desflurane took an intermediate position.*

Results. *The use of desflurane as an inhalation anesthetic in a kidney transplant provided a quicker recovery of consciousness and early extubation of the patient after anesthesia compared to the sevoflurane or isoflurane use. So desflurane proved to be the most efficient of the three studied inhalation anesthetics.*

Conclusion. *Desflurane is the optimal inhalation anesthetic used in kidney transplantation.*

Keywords: desflurane, inhalation anestetics, kidney transplantation

BP, blood pressure

CKAT, cadaveric kidney allotransplantation

CKD, chronic kidney disease

CVS, cardiovascular system

DBP, diastolic blood pressure

ECG, electrocardiogram

ESRD, end-stage (chronic) renal disease

EtO_2, end-tidal O_2 concentration in expired gas mixture

FG, fresh gas

GFR, glomerular filtration rate

HR, heart rate

IA, inhalation(al) anesthetics

KT, kidney transplantation

MAC, minimum alveolar concentration

O_2, oxygen

SBP, systolic blood pressure

SpO_2, blood oxygen saturation

Introduction

The end-stage chronic renal disease (ESRD) is a consequence of various, usually chronic, diseases: chronic glomerulonephritis, chronic pyelonephritis, interstitial nephritis, hereditary vascular abnormalities, and cystic disease. Every year, the number of patients with ESRD is increasing. According to the Russian Registry database, 41 kidney transplantation centres function in our country. The waiting list for kidney transplantation (KT) in Russia includes 5600 patients accounting for approximately 13.8% of the total number of patients on program dialysis [1]. There are about 750 candidates for kidney transplantation on the waiting list of N.V.Sklifosovsky Institute for Emergency Medicine. About 200 kidney transplantations from post-mortem donors are performed annually in its Kidney and Pancreas Transplantation Department.

Cadaveric kidney allotransplantation (CKAT) is a definitive treatment of ESRD, which improves the patients' quality of life and life expectancy [2].

Patients with ESRD, as a rule, have comorbidities that may cause high anesthetic risks. Patient's physical status was scored 5 and assessed as Degree IV (high risk) according to the Operative and Anesthetic Risk Classification developed by Moscow Scientific Society of Anesthesiologists and Critical Care Physicians. For the normal graft

functioning, the blood pressure (BP) should be maintained normal, or high at some stages of surgery, throughout the entire period of the anesthesia provision. A correct selection of anesthesia components (the choice of an effective inhalation anesthetic, IA), the tactics of infusion therapy in CKAT have an effect on the primary function of a transplanted kidney graft [3].

The aim of the study was to compare the efficacies of IAs used for cadaveric kidney allotransplantation.

Material and methods

The prospective, single-centre, randomized study that was conducted in N.V.Sklifosovsky Research Institute for Emergency Medicine from January 1 to July 1, 2019, included 62 patients with stage 5 chronic kidney disease (CKD) (glomerular filtration rate [GFR] was lower than 15 mL/min/173m^2 as assessed by MDRD formula). CKAT was successfully performed in all patients. Patients were allocated into three groups according to the intraoperative IA used: group I included 22 patients for whom desflurane was used as IA, group II and group III included 20 patients each, for whom sevoflurane or isoflurane was used, respectively. The random distribution method was used for making the investigation.

Inclusion criteria in the study:

1. Cadaveric kidney allotransplantation under conditions of combined endotracheal anesthesia in patients with stage 5 CKD (GFR lower 15 mL/min/173 m^2 as assessed by MDRD formula), regardless of the underlying pathology;
2. The patient age from 18 to 65 years old;
3. The patient extubated on the operating table on CKAT completion;

4. The administration of muscle relaxant (cisatracurium besylate) discontinued no less than 29–40 minutes before the termination of the IA use.

The assessed parameters were age, gender, height, weight, cold ischemia time.

There were no statistically significant differences between the compared groups in patient gender, height, and weight ($p>0.05$), no differences were noted in the cold ischemia time of donor kidney, either ($p=0.1$) (Table 1).

Table 1. Characteristics of recipient groups

Parameter	Recipient groups			P
	Desflurane, n = 22 (Me (1; 3))	**Sevoflurane, n = 16 (Me (1; 3))**	**Isoflurane, n = 14 (Me (1; 3))**	
Age, years	50 (45; 58)	48 (41; 53.5)	46 (39; 50)	0.557
Gender, male/female	7/15	9/7	7/7	0.226
Height, cm	175.5 (169; 180)	173 (170; 180)	167 (163; 171)	0.065
Weight, kg	80.1 (66; 84)	69.5 (64; 92.7)	70.5 (65; 82)	0.931
Donor organ ischemia time, min	885 (760; 930)	780 (722.5; 890)	825 (720; 870)	0.109

Tactics of providing anesthesia

Induction anesthesia was provided with propofol at a dose of 2–2.5 mg/kg in combination with fentanyl 5 μg/kg, followed by administering cisatracurium besylate at a dose of 150 μg/kg. After the muscle relaxant infusion, a tracheal intubation was performed and the mechanical lung ventilation was started (IA delivery). Primus Dräger® anaesthesia machine with semi-closed circuit was used.

Inhalation anesthetics were given in the following concentrations: desflurane at 12.0 vol.% (fresh gas (FG) flow rate of 2 L/min in the circuit); sevoflurane at 4.0 vol.% (FG flow rate of 4 L/min in the circuit); isoflurane at 2.4 vol.% (FG flow rate of 4 L/min in the circuit) until achieving the saturation equal to 1.0 minimum alveolar concentration (MAC) vol.%. After achieving MAC of 1.0 vol.%, IA was administered according to the minimal flow anesthesia principle in the desflurane group (FG flow rate in the circuit not exceeding 0.5 L/min), the FG flow rate was 2 L/min in the sevoflurane group, and 1.5 L/min in the desflurane group.

The main hemodynamic parameters (heart rate [HR], blood pressure) were monitored; the acid-base status and water-electrolyte balance parameters were assessed in venous blood samples.

Pulse oximetry parameters, the episodes of rhythm disturbance, tachycardia (heart rate over 90 beats/min), bradycardia (heart rate lower 60 beats/min), hypotension (BP_{syst} lower 80 mm Hg) were also considered. The BP values were recorded at the stage of the skin incision and pre-arterial/venous reperfusion of the donor organ - I and II periods of anesthesia - from the stage of nephrotransplant reperfusion to surgery completion.

After patient's emergence from anesthesia and the provided decurarization (administering atropine at a dose of 0.01 mg/kg; galantamine hydrobromide, 20 mg), the time intervals were estimated: till patient's opening the eyes, squeezing a hand, extubation, and uttering the date of birth. The transplanted kidney function was assessed by measuring the hourly urine output and the urine amount after the kidney allograft reperfusion.

Statistical analysis

Parametric and nonparametric statistics methods were used for data analysis. The data analysis results are presented as means with standard deviations, medians and inter-quartile ranges. A variance analysis of three groups with an independent distribution was made (Kruskell–Wallis test), and the χ^2 was calculated. To compare the data results before and after the IA administration, the Wilcoxon test was used. P values <0.05 were considered statistically significant. Statistical analysis was performed using Statistica 10.0 software package.

Results

Data showing the total doses of the drugs used to maintain anesthesia, the time of IA saturation, the oxygen fraction (O_2) on inspiration until achieving SpO_2 of 98–100%, are presented in Table 2.

Table 2. Comparative characteristics of the consumption of muscle relaxants, fentanyl and anesthetic saturation time

Parameter	Recipient groups			P
	Desflurane, n = 22 (Me (1; 3))	Sevoflurane, n = 16 (Me (1; 3))	Isoflurane n = 14 (Me (1; 3))	
Muscle relaxant, total dose, mg	30 (25; 30)	30 (25; 35)	30 (25; 32.5)	0.094
Fentanyl, total dose, mg	0.8 (0.7; 0.9)	0.8 (0.7; 0.38)	0.8 (0.8; 0.9)	0.305
Anesthetic saturation time to MAC 1.0 vol.%, min	4 (3; 4)	4 (4; 5)	5.25 (5; 8)	0.001
EtO_2, %	50 (50)	50 (50)	50 (50; 55)	0.809

Table 2 shows no statistically significant differences between the groupsin the amounts of administered cisatracurium besylate, fentanyl, and the O_2 fraction (SpO_2 = 98–100%) ($p>0.05$). The IA saturation time to MAC of 1.0 vol.%, at a similar flow rate, was minimal in the desflurane group, and maximal in the isoflurane group ($p<0.05$, statistically significant).

The results of comparing the side effects on the cardiovascular system (CVS) are shown in the Figure. Under the impact of desflurane, rhythm disturbances (solitary ventricular extrasystoles undetectable at electrocardiogram (ECG) before surgery) were found in 4.5% of patients and were absent when other IAs were used ($p<0.05$, statistically significant). The incidence rates of tachycardia (50%) and hypotension episodes (5%) were the highest with sevoflurane; and bradycardia episodes (7.5%) occurred more often with isoflurane ($p<0.05$, statistically significant).

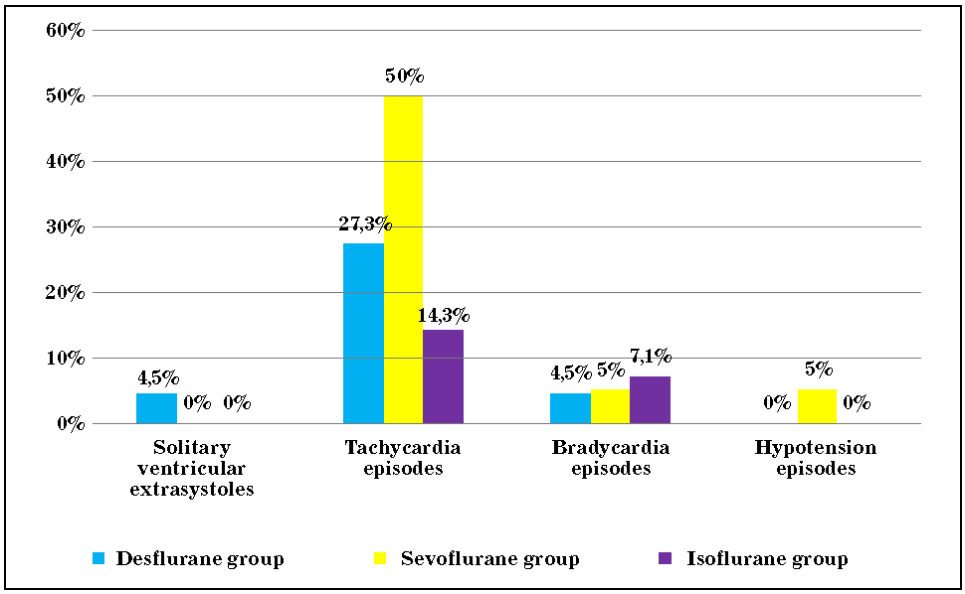

Figure. The incidence of side effects on the cardiovascular system when using various anesthetics, %

A statistical significance was revealed between the IA use and the effect on hemodynamic parameters. We compared the changes in BP and HR over time:

1. From the time of induction anesthesia to reperfusion;
2. Before reperfusion and after the emergence from anesthesia.

Tables 3-5 show the values characterizing the changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate over time in the patients of groups I, II, and III. The SBP and DBP changes over time were statistically significantly different when using all IAs both in the 1st and 2nd periods of anesthesia; the observed changes in SBP and DBP were the greatest when using isoflurane, and the smallest with sevoflurane ($p < 0.05$). Heart rate variability occurred with the use of isoflurane and was minimal when desflurane or sevoflurane was used ($p < 0.05$, statistically significant in both cases).

Table 3. Changes in blood pressure over the time interval from the moment before induction anesthesia till the start of reperfusion

IA Group	BP before induction anesthesia (mean±SD)		BP before reperfusion (mean±SD)		P
	SBP, mm Hg	DBP, mm Hg	SBP, mm Hg	DBP, mm Hg	
Group I	146.8±16.9	83.4±11.4	114.8±20.6	67±15.1	<0.05
Group II	139.3±19.8	84.7±14.6	126±17.6	74±16.8	<0.05
Group III	152.5±12.8	89.3±12.8	117.9±11.2	69.1±10.7	<0.05

Table 4. Changes in blood pressure over the time interval from the moment before the start of reperfusion till the end of surgery

IA Group	BP before reperfusion (mean±SD)		BP after reperfusion (mean±SD)		P
	SBP, mm Hg	DBP, mm Hg	SBP, mm Hg	DBP, mm Hg	
Group I	114.8±20.6	67±15.1	138.9±12.9	88.4±10.7	<0.05
Group II	126±17.6	74±16.8	142±13.2	89.4±11	<0.05
Group III	117.9±11.2	69.1±10.7	139.2±14.4	79.2±6.4	<0.05

Table 5. Changes in the heart rate over time at surgery stages

IA Group	Heart rate before induction anesthesia (mean±SD)	Heart rate after the start of anesthesia (mean±SD)	P	Heart rate before reperfusion (mean±SD)	Heart rate after reperfusion (mean±SD)	P
Group I	83±11.4	64.8±5.6	0.00	64.8±5.6	72.9±11.1	0.246
Group II	82.4±13.5	72.2±12.5	0.02	72.2±12.5	75.5±15.5	0.439
Group III	82.8±12.9	67.9±10.3	0.001	67.9±10.3	77.6±14.4	0.024

Isoflurane had the greatest impact on hemodynamics; the most stable hemodynamic parameters were observed with sevoflurane use, and desflurane took an intermediate position by this parameter ($p<0.05$, statistically significant).

Table 6 shows temporal data on the recovery of consciousness and muscle tone. The "awakening" time was characterized by opening the eyes, by the recovery of the muscle tone (the ability of squeezing a hand), and that of consciousness (the ability of uttering the date of birth). The emergence from anesthesia, the recovery of consciousness and muscle tone occurred most rapidly after using desflurane, and were the longest with isoflurane ($p <0.05$), which facilitated an earlier extubation in group

I. Meanwhile, sevoflurane took an intermediate position ($p < 0.05$, statistically significant in both cases).

Table 6. Temporal indicators of the recovery of consciousness and muscle tone after anesthesia

Parameter	Recipient groups			P
	Desflurane , n = 22 (Me (1; 3))	Sevoflurane , n = 20 (Me (1; 3))	Isoflurane, n = 20 (Me (1; 3))	
Opening the eyes, min	3,5 (2; 5)	5,9 (3; 7)	8,6 (3; 9)	0,045
Squeezing a hand, min	4,7 (3; 6)	6,8 (4; 9)	9,2 (4; 9)	0,02
Extubated, min	5,3 (3; 6)	7,9 (4; 10)	10 (5; 10)	0,014
Uttering the date of birth, min	6,7 (5; 8)	8,8 (6; 11)	11,3 (6; 12)	0,02

Discussion

Inhalational anesthetics produce different effects both on systemic hemodynamics and microcirculation, including those of kidneys [4]. According to different authors, IAs may vary in the extent of their potential nephrotoxicity. So, currently sevoflurane is the most commonly used IA. A number of investigators have reported of sevoflurane-related nephrotoxicity, despite a widespread opinion of its having no properties that could have caused a kidney dysfunction [5]. A small part of administered sevoflurane is subjected to metabolism, resulting in the formation of an inorganic fluoride ion that irreversibly binds to methoxyflurane, thereby causing toxic effects on kidneys [6–8]. In addition, substance A, another product of the sevoflurane metabolism, is

formed that in the presence of carbon dioxide can both affect the respiratory centre, leading to the development of postoperative apnoea syndrome, and cause kidney injury in animals [9, 10]. Though, some authors have reported a protective effect of sevoflurane and its metabolites on the renal graft [11, 12].

The isoflurane use as an IA leads to a more pronounced vasodilation compared to other IAs, which determines the tendency to tachycardia development and a decrease in systemic blood pressure. This can also be accompanied by a decreased renal blood flow, GFR and, as a consequence, by reduced intraoperative diuresis at the stage of reperfusion [13].

At the same time, the results obtained in a number of studies have proved the advantage of isoflurane in KT. So, Yildirim et al. demonstrated that the blood serum level of urea was higher and diuresis was lower with using sevoflurane compared to the data obtained when using isoflurane [4].

In recent years, desflurane has been implemented in anesthetic practice as the IA that, according to many criteria, has advantages over other drugs of this group. In some randomized clinical trials, desflurane properties (its effect on the emergence from anesthesia assessed by the time to opening the eyes, extubation and recovery of consciousness) were compared with those of other IAs when used in general surgery interventions for various diseases, but its potential effect on the anesthesia course and surgery outcome in KT has not been studied yet [14]. According to the results of other studies, the emergence from anesthesia after surgery was faster with desflurane than with other IAs [15, 16]. Bellgardt et al. reported that the patient was extubated faster after anesthesia with desflurane (time to extubation was 5.27 ± 1.59 min) compared to the same parameters for sevoflurane (6.19 ± 2.56 min) and

isoflurane (9.31 ± 6 04 min) [17]. The results of our study showed statistically significant faster emergence, greater opportunities for extubation, as well as recovery of brain cognitive functions when using desflurane compared to sevoflurane and isoflurane.

Various authors investigated the IA impact on hemodynamics; and at the same time they revealed a number of side effects on CVS. As reported, no statistically significant differences were found in the incidence of arterial hypotension and hypertension resulting from the use of desflurane and sevoflurane [18]; mean blood pressure and heart rate were similar in these groups [19]. The results of the present study showed a more frequent occurrence of tachycardia and hypotension episodes with sevoflurane use, while bradycardia episodes were more often recorded with isoflurane.

Another study reported abnormal ECG signs: the height of the P wave increased, and the duration of the QT interval compared with the baseline increased significantly with the desflurane induction, but that increase did not cause any dangerous arrhythmias [20]. In our study, solitary ventricular extrasystoles were recorded only in one case (4.5%) of using desflurane.

Conclusions

1. The use of desflurane allows a sooner patient extubation with adequate recovery of consciousness and a quicker emergence from anesthesia, which is important both for reducing the time spent in the operating room and for faster postoperative rehabilitation.

2. The most significant impact on systemic hemodynamics is observed in isoflurane, therefore, the clinical use of this inhalational anesthetic for kidney transplantation is undesirable, thereby determining the choice in favour of desflurane and sevoflurane.

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