INTRODUCTION

The programme of kidney transplantation in Latvia was started in 1973. The growing number of kidney transplants during the subsequent period raised new aspects in anaesthetic management. It was found that the incidence of post-operative acute tubular necrosis or delayed graft function after cadaveric transplantation depends on many factors and one of them is haemodynamic stability during reperfusion of transplant. For renal transplantation, the major anaesthetic consideration is maintenance of renal blood flow. Typical haemodynamic goals during reperfusion are systolic blood pressure (SBP) above 120–130 mm Hg and target central venous pressure (CVP) ≥ 10–12 mm Hg. Below these values, there is an increased incidence of acute tubular necrosis (Akpek et al., 2002; Thomas et al., 2003; Pericol et al., 2004). Taking into account that during anaesthesia there is interaction between intravenous induction agents, inhalational anaesthetics and haemodynamics, this study aimed to provide an overview and critical analysis of past anaesthetic management for renal transplantation, based on 40 years of clinical experience. The main aim of this study was to evaluate the haemodynamic effects of different anaesthesia methods, with focus on time of graft revascularisation and kidney survival.

GENERAL ANAESTHESIA FOR RENAL TRANSPLANTATION IN LATVIA: A CRITICAL ANALYSIS BASED ON CLINICAL EXPERIENCE


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Communicated by Rafails Rozentāls

Anesthesia methods for surgical procedures, as well as for organ transplantation, have experienced remarkable changes over the past 40 years. Cadaveric renal transplant function may be impaired by haemodynamic instability induced by anaesthesia drugs. This study aimed to analyse the safety and effectiveness of the different anaesthesia methods used for renal transplantation in Latvia since 1973, with focus on its haemodynamic effects. In this retrospective study anaesthesia chart review was conducted for 607 patients (pts), aged 17–75 yrs, ASA III/IV, undergoing renal transplantation using general anaesthesia in the following periods: 1973–1990 (stage I – 282 pts); 1991–2000 (stage II – 145 pts); 2001–2011 (stage III – 180 pts). Haemodynamic data (systolic, diastolic, mean arterial blood pressure and central venous pressure) were measured prior to premedication and induction of anaesthesia, immediately afterwards, during the surgery and up to its completion with the special attention regarding the time of graft reperfusion. The main perioperative problems of the anaesthesia methods used during stage I (barbiturates, viadril, neuroleptanalgesics, sodium oxybutyrate, halothane, nitrous oxide) was haemodynamic instability in 60% of cases and apnea due to central depression and long-time peripheral neuromuscular blockade. Two patients died due to underlying comorbid conditions, including hyperhidration and oedema pulmonum. Substantial haemodynamic changes during total intravenous anaesthesia with propofol and combined anaesthesia propofol-isoflurane (stage II) were not observed. At the time of graft reperfusion, the incidence of hypotension was slightly higher in patients anaesthetised with isoflurane than in those who received sevoflurane (stage III), but this difference was not significant (P > 0.05). Kidney functioned immediately in 75% of cases and delayed function was observed in 25% of cases in sevoflurane and isoflurane groups. The modern anaesthetic agents provide a great margin of safety during renal transplantation. Total intravenous anaesthesia with midsalolam-fentanyl-propofol and general anaesthesia with propofol-isoflurane, propofol-sevoflurane can be safely used. During renal transplantation, anaesthesiologists must optimise volume status, perfusion pressure and promote survival of the renal graft.

Key words: anaesthesia, renal transplantation.
MATERIALS AND METHODS

After approval by the hospital Ethics Committee a retrospective anaesthesia chart review was conducted for patients undergoing renal transplantation using general anaesthesia. After approval by the hospital Ethics Committee a retrospective anaesthesia chart review was conducted for patients undergoing renal transplantation using general anaesthesia. After approval by the hospital Ethics Committee a retrospective anaesthesia chart review was conducted for patients undergoing renal transplantation using general anaesthesia. After approval by the hospital Ethics Committee a retrospective anaesthesia chart review was conducted for patients undergoing renal transplantation using general anaesthesia.

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METHODS OF GENERAL ANAESTHESIA FOR RENAL TRANSPLANTATION IN 282 PATIENTS IN 1973–2000

<table>
<thead>
<tr>
<th>Direct premedication</th>
<th>Agents for induction, n, number of patients</th>
</tr>
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<tbody>
<tr>
<td>Diazepam 5–10 mg;</td>
<td>Viadril 1–0 g (n = 24);</td>
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<tr>
<td>Atropin 0.5–0.8 mg;</td>
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<tr>
<td>Promedol 20 mg;</td>
<td>Thiopeptal 3–4 mg/kg with fentanyl and droperidol (n = 142);</td>
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<tr>
<td>Dimedrol 20 mg (standardised for all patients) i/v</td>
<td>Sodium oxybutyrate, 2.0–4.0 g, combined with thiopeptal 0.1–0.2 g (n = 96);</td>
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<td></td>
<td>Neuroleptanalgesia (NLA): droperidol 12.5–17.6 mg, fentanyl 0.25–0.4 mg + N2O (n = 20)</td>
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<table>
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<tr>
<th>Agents for maintenance</th>
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<tbody>
<tr>
<td>Nitrous oxide (N2O), combined with i/v NLA, (n = 252);</td>
<td></td>
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<tr>
<td>Halothane or its combination with ether combined with fentanyl (n = 30)</td>
<td></td>
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<tr>
<th>Neurromuscular blocking drugs (NMBD)</th>
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<tbody>
<tr>
<td>Succinylcholine,</td>
<td></td>
</tr>
<tr>
<td>Dioxonium,</td>
<td></td>
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<tr>
<td>d-tubocurarine</td>
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In all patients of the three stages of study, preoperative haemodialysis was provided 24–48 h before renal transplantation. Before surgery and anaesthesia, patients underwent full medical and surgical history and routine laboratory investigation (i.e. blood Hb, Ht, plasma proteins, coagulation tests, biochemical tests and serum electrolytes, blood glucose, chest radiograph and electrocardiography) and were evaluated by anaesthesiologists. In 15 patients with ESRD severe anaemia, blood samples for electronic microscopy of erythrocytes were detected and identified as the potential cause of dramatically changes of shape of erythrocytes that accompanied severe anaemia; many codocytes, stomatocytes, and echinocytes were detected and identified as the potential cause of severe arterial hypertension with SBP that varied from 170 to 230 mm Hg (180 ± 20 mm Hg) and diastolic blood pressure (DBP) greater than 110 mm Hg (112 ± 15 mm Hg). Study of erythrocyte morphology (by Dr. habil. biol. Velta Ose, Institute of Microbiology, personal communication) revealed dramatic changes of shape of erythrocytes that accompanied severe anaemia; many codocytes, stomatocytes, and echinocytes were detected and identified as the potential cause of blood reology disorders due to deformity and rigidity (Fig. 1). After induction of anaesthesia with barbiturates and neuromuscular blocking agents, SBP decreased significantly in all hypertensive patients by 40 ± 20% (P < 0.05) compared with the premedication induction of anaesthesia and just before induction of anaesthesia. Occasionally, a low-dose dopamine infusion (2–4 µg/kg/min) was used to increase blood pressure and improve perfusion of graft. Kidney turidity was evaluated by the surgical team members for assessment of the hydration regimen.

Haemodynamic parameters were measured prior to premedication and induction of anaesthesia, immediately afterwards, and during anaesthesia up to end of surgery, with the special attention to the time of graft reperfusion. Cardiovascular instability was determined by measuring changes in excess of 20% of basal systolic blood pressure (SBP) after induction of anaesthesia and < 95 mm Hg at the reperfusion time. The incidence in percentage (%) of severe hypertension and hypotension after induction of anaesthesia and just after reperfusion, as well as CVP at time of declamping was recorded. The total volume of fluids and restoration of transplant function (immediate, delayed and non-function) were controlled. All patients after completion of surgery were observed carefully for signs of residual myorelaxation, fluid overload and dehydration. The hourly urine output was replaced with normal saline 1 mL for each mL of urine.

With the aim to investigate the relationship between the use of potentially nefrotoxic inhalation anaesthetic sevoflurane and recovery profiles of kidney function the incidence of immediate, delayed graft function as well non-function was analysed in 12 patients who developed arterial hypotension with SBP up to 95–85 mm Hg at the time of reperfusion. These data were compared with the same parameters of the isoflurane group. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS 14.0). Demographic and perioperative data were compared using the Student’s t-test. A value of P < 0.05 was taken as statistically significant.

RESULTS

Stage I. The retrospective study found that 40% of involved patients were anaemic with Hb 7% and Ht 20%, with hypoproteinaemia. 80% of the recipients demonstrated initial severe arterial hypertension with SBP that varied from 170 to 230 mm Hg (180 ± 20 mm Hg) and diastolic blood pressure (DBP) greater than 110 mm Hg (112 ± 15 mm Hg). Study of erythrocyte morphology (by Dr. habil. biol. Velta Ose, Institute of Microbiology, personal communication) revealed dramatic changes of shape of erythrocytes that accompanied severe anaemia; many codocytes, stomatocytes, and echinocytes were detected and identified as the potential cause of blood reology disorders due to deformity and rigidity (Fig. 1). After induction of anaesthesia with barbiturates and neuromuscular blocking agents, SBP decreased significantly in all hypertensive patients by 40 ± 20% (P < 0.05), compared with the

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**Table 2**

<table>
<thead>
<tr>
<th>Patient group, n</th>
<th>Induction of anaesthesia</th>
<th>Maintenance of anaesthesia</th>
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</thead>
<tbody>
<tr>
<td>Isoflurane group, n = 80</td>
<td>Propofol 1.6–2.2 mg/kg, Fentanyl 1.5–2.0 mg/kg, Atracurium 0.5 mg/kg</td>
<td>Isoflurane (0.8–1 MAK) + supplementary doses of fentanyl (0.1 mg)</td>
</tr>
<tr>
<td>Sevoflurane group, n = 90</td>
<td>Propofol 1.6–2.2 mg/kg, Fentanyl 1.5–2.0 mg/kg, NMBA 0.5 mg/kg</td>
<td>Sevoflurane (0.8–1 MAK) + supplementary doses of fentanyl (0.1 mg)</td>
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**Table 3**

<table>
<thead>
<tr>
<th>Patient group, n</th>
<th>Induction of anaesthesia</th>
<th>Maintenance of anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane group, n = 65</td>
<td>Propofol 1.6–2.2 mg/kg, Fentanyl 1.5–2.0 mg/kg, Atracurium 0.5 mg/kg</td>
<td>Isoflurane (0.8–1 MAK) + supplementary doses of fentanyl (0.1 mg)</td>
</tr>
<tr>
<td>Sevoflurane group, n = 120</td>
<td>Propofol 1.6–2.2 mg/kg, Fentanyl 1.5–2.0 mg/kg, NMBA 0.5 mg/kg</td>
<td>Sevoflurane (0.8–1 MAK) + supplementary doses of fentanyl (0.1 mg)</td>
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</table>
initial level. Immediately after tracheal intubation and during the early postintubation period, all hypertensive patients given nitrous oxide for maintenance of anaesthesia remained hypertensive during the operation and anaesthesia. However, careful administration of halothane seemed to be the most favourable method for controlling haemodynamic stability in hypertensive patients. We did not find any evidence that halothane deteriorated kidney function. The use of a combination of barbiturates with sodium oxybutyrate or sodium oxybutyrate alone for induction prevented significant hypotension in normotensive patients. The steroid anaesthetic viadril demonstrated a moderate hypotensive effect (15–17% of patients) and was an appropriate agent for induction in hypertensive patient. Unfortunately, this drug caused irritation of venous walls and induced local tromboembolism. Significant harmful effect of the used methods of anaesthesia on haemodynamic at time of graft reperfusion moment was not shown. The main perioperative complications during this stage of anaesthesia system development was haemodynamic instability, which occurred in 60% of cases. Apnea due to central depression and peripheral neuromuscular blockade with prolonged artificial ventilation for 2–6 hrs after the end of surgery was detected in 1.8% of patients. Two patients died due to underlying comorbid conditions, including hyperhydration and oedema pulmonum.

In conclusion: in this stage the same anaesthetics and analgesics were used for renal transplantation in Latvia as were used worldwide. It was possible to carry out anaesthesia during renal transplantation using the combination of non-inhalation and inhalation anaesthetics, the selection of which was dependent on the excretory function of kidneys of recipients and also haemodynamic data. However, there was no optimal method of anaesthesia. The main problem was inability to use a safe muscle relaxant not requiring renal function for its elimination. Unfortunately, use of succinylcholine was limited due to its known hyperkalemic effect and potential cardiac arrest.

Stage II. The demographic characteristics of the recipients and their corresponding donors as well as donor organ cold ischemia and duration of surgery did not differ significantly between the two groups of this study stage. Patients of both groups had similar haemodynamics. Arterial hypertension was detected in both groups. In 75% of cases SBP exceeded 170 mm Hg and was on average 180 ± 15%, DBP – 95 ± 10 mm Hg. In 61 patients with severe arterial hypertension (41.03%), myocardial hypoxia was detected on ECG. Premedication with the sedative drug midasolam (in average 2.5 mg) and strong opioid fentanyl (0.15–0.2 mg), and careful use of a sleeping dose of propofol by titration method (120–200 mg) provided uncomplicated induction in anaesthesia and endotracheal intubation in all patients. Midasolam-propofol induction resulted in decrease of SBP by 18 ± 5%, compared with the initial level. In TIVA group by careful titrating of propofol infusion it was possible to stabilise and regulate arterial pressure at the necessary level (12–16% under initial) throughout, and to increase the level during graft reperfusion. We did not observe substantial haemodynamic changes during anaesthesia, nor after kidney reperfusion. Adequate anaesthesia was obtained by an intravenous dosing of 450 ± 100 mg propofol, 0.5–0.7 mg fentanyl, and 110 ± 20 mg atracurium. Recovery was rapid and occurred 11 ± 4 min after end of infusion. None of the patients experienced nausea and vomiting. The patients achieved and maintained high recovery scores. A high proportion of immediate graft function was achieved. In conclusion: propofol has been successfully used for total intravenous anaesthesia for kidney transplant surgery, and was associated with a reduction in postoperative nausea and vomiting.

Isoflurane in concentration 0.8–1 MAK for maintenance of anaesthesia induced moderate vasopliceg and hypotensive effect. SBP was stabilised at a 17 ± 5% level and DBP at a 10 ± 6% level under initial. The study found no significant difference in haemodynamic changes between TIVA and isoflurane groups during renal transplantation (P > 0.05). However, isoflurane improved peripheral circulation more than propofol. Peripheral temperature was 0.8–1°C higher in the isoflurane group in comparison with the propofol group.

In conclusion: combined general anaesthesia with isoflurane produced excellent conditions for the operation with rather prompt recovery after 16 ± 5 min. The recovery period was slightly longer than in the propofol group, which may be explained by intensification of muscle relaxant effect. In these two groups sufficient renal blood perfusion in the graft was achieved. However, the main postoperative problem in the isoflurane group was shivering as a consequence of vasodilatation. Results of the study shown that isoflaure-like propofol may be an agent of choice for renal transplantation.

Stage III. The demographic and clinical characteristics of the patients involved in the study are given in Table 4.

There were no significant differences between groups with respect to demographic characteristics of the recipients and incidence of severe and moderate hypertension before sur-

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Fig. 1. Electronic microphotograph of erythrocytes of the patients with end-stage renal disease due to diabetic nephropathy in comparison with normal erythrocytes.

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Surgery and anaesthesia. The proportion of normotensive patients was lower in the sevoflurane group. Data on the haemodynamic reaction to combined general anaesthesia with propofol-isoflurane and propofol-sevoflurane are given in Table 5.

Arterial blood pressure decreased significantly (in excess of 20% of basal systolic blood pressure, $P < 0.05$) after induction with propofol-midazolam-fentanyl in both groups of patients, but no patients developed severe arterial hypertension due to arterial hypertension before surgery. A significant difference between groups was not detected in hypotensive reaction to induction of anaesthesia and immediately afterwards. At the time of graft reperfusion the incidence of hypotension was seen in 25%. There were no differences between groups.

DISCUSSION

Successful treatment of patients with ESRD by kidney transplantation cannot be carried out without taking into consideration the perioperative anaesthetic management and strategies. The effect of drugs on recipient, the effect of drugs on the function of the transplanted kidney and the effect of drugs that depend on the transplanted kidney for their elimination should be taken into account (Sondore et al., 1994). Patients with ESRD present many problems to the anaesthesiologists. The majority of patients suffer from some degree of hypertension and may be on antihypertensive drug therapy. Hypotension may occur during anaesthesia due to interaction of antihypertensive drugs and due to haemodynamical effects of anaesthetics. Hypovolaemia must be avoided, as hypotension increases the possibility of acute tubular necrosis in the transplant (Carlier et al., 1982; O’Malley et al., 2002; Hadimioglu et al., 2008; Othman et al., 2010). In stage I of the kidney transplant development in the period 1973 to 1990, viadril, barbiturates, sodium oxybutyrate, and neuroleptanalgesia were used for induction of anaesthesia, while for maintenance the volatile anaesthetics nitrous oxide and halothane with opioid fentanyl and different available muscle relaxants, including long-acting, were used. Nitrous oxide has not been shown to have any effects on the kidney function, but in anaemic patients with ESRD it may seriously impair the oxygen-carrying capacity (Mazze et al., 1974). Therefore, use of nitrous oxide for anaesthesia in transplants was later avoided and in some cases contraindicated. Halothane in stage I of clinical experience was probably the most widely used volatile anaesthetic. Unfortunately, halothane was not an ideal anaesthetic also due to potential hepatotoxic effect and high metabolic rate. The main perioperative complications of that period were haemodynamic instability during anaesthesia (in 60% of cases) and apnea due to central depression and peripheral neuromuscular blockade with need for prolonged postoperative artificial ventilation. Two patients died due to underlying comorbid conditions, including hyperhydration and oedema pulmonum.

In stage II, propofol was successfully implemented for total intravenous anaesthesia for kidney transplantation. Smooth, rapid induction and rapid clear headed recovery should be mentioned among the advantages of propofol. However, it may decrease arterial pressure, cardiac output and systemic vascular resistance. No patients in the TIVA group developed severe arterial hypotension. By careful titrating of propofol infusion arterial pressure was stabilised on the necessary level. Substantial haemodynamic changes at the time of graft reperfusion were not seen.

As most of the recipients were hypertensive, intravenous opioids such as fentanyl, were usually used not only for analgesia, but also with the aim to blunt the stress response to laryngoscopy and tracheal intubation. Its excretion is...
mainly by hepatic metabolism. In our study fentanyl was successfully used in normal doses (Koehntop and Rodman, 1997). The non-depolarising relaxant atracurium has advantages, as it is broken down by Hofmann degradation. It was the main drug of choice for muscle relaxation in our study.

Haemodynamic changes that accompany TIVA were observed in the isoflurane group “a”. Minimal metabolism (0.2%), lack of toxicity, improvement of coronary and peripheral circulation, and decreased requirement for muscle relaxants make isoflurane a suitable drug for anaesthesia in patients with ESRD. In accordance with published data, it has less effect on cardiac output and renal blood flow than another anaesthetics. However, hypotension that may develop during isoflurane anaesthesia should be taken into account.

During stage III of clinical renal transplantation, the volatile agent sevoflurane has been used in patients undergoing renal transplantation. Some authorities do not recommend sevoflurane for anaesthesia during renal transplantation. It has been considered undesirable due to potential toxic fluoride accumulation after 2–4 h of anaesthesia. However, most studies have not found any detectable postoperative impairment of renal function using this drug (Kharasch et al., 1997). We did not observe any harmful effect of sevoflurane on kidney transplantation outcome. Comparative evaluation of kidney function in the sevoflurane and isoflurane groups showed no differences in immediate or delayed function. The immediate start of diuresis was found in 75%, delayed in 25%, and non-function was not seen in both groups.

The conclusion is that adequate renal blood flow is essential for good donor kidney function. Good perfusion of the new kidney is dependent on adequate intravascular volume and the avoidance of hypotension. Controversy exists regarding the optimal anaesthesia method for renal transplantation. Optimisation of the anaesthesia method in Latvian Centre of Renal Transplantation has been ongoing along with the development of pharmacology for anaesthesiology. Our clinical experience demonstrated that general anaesthesia can be safely provided by carefully induced intravenous induction agents, preferably propofol, given slowly after premedication with benzodiazepine midazolam and opioid fentanyl. Maintenance of general anaesthesia can be satisfactorily achieved by total intravenous anaesthesia using propofol as the main anaesthetic, as well as with inhalational anaesthetics isoflurane and sevoflurane. During renal transplantation, anaesthesiologists must optimise volume status, perfusion pressure and promote survival of the renal graft.

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Received 11 December 2012


Received 11 December 2012


VISPĂRÇJA ANESTĒZIJA NIERES TRANSPLANTÂCIJÂ LATVIJÂ: KRITISKA ANALÎZE, BALSTÎTA UZ KLÎNISKO PIEREDZI


Vispārējā intravenozā anestēzija ar propofola infuziju un vispārējā anestēzija ar propofolu-izoflurānu (II etaps) ievērojumus hemodināmiskajās reakcijās neizrādīja. III etapā gūtā pieredze apliecina, ka transplantāta reperfūzijas laikā izoflurāna anestēzijai piemīt lielāks hipotensorais efekts salīdzinājot ar sevoflurānu, bet šī stārpiba nebija statistiski ticama (P < 0.05). Abās pacientu grupās transplantāta primārā funkcija tika reģistrēta 75%, bet attīstīt — 25% gadījumu. Vispārējā anestēzija ar moderniem anestēzijas līdzekļiem un metodēm, lietojot propofola infuziju kombinācijā ar benzodiazepīnu midazolāmu un opioidu fentanīlu, kā arī vispārējā kombinētā anestēzija ar propofolu-izoflurānu, propofolu-sevoflurānu, benzodiazepīnu midazolāmu un opioidu fentanīlu var nodrošināt īpašu perioperatīvās aprūpes nieru transplantācijas laikā. Īpaša uzmanība jāpievērš svarīgajai pārstādītai nieres funkcijas garantīm — pacienta volēmijas stāvoklim un transplantāta perfūzijas spiedienam asinsrites atjaunošanas momentā.