Anesthesia for renal transplantation-A review

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Abstract
A patient with end-stage renal disease scheduled for renal transplantation presents to the anesthesiologist with many clinical problems. These patients present a unique set of challenges to the anesthetist, who has a crucial role in the immediate success of the transplanted organ. A successful outcome depends on a clear understanding of the clinical issues of renal failure and the choice of an appropriate anesthetic technique for renal transplantation.

This article describes the assessment of the patient for renal transplantation, perioperative management and the goals in the postoperative period.

Keywords
Anesthesia; Transplantation; Renal

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Review
**Introduction**

Patients with end-stage renal failure for whom renal transplantation is planned pose several clinical problems for anesthetists. The important steps for successful anesthesia are good understanding of the clinic of renal failure, knowing the effects of renal failure on pharmacokinetics, metabolism and pharmacodynamics, proper management of other systemic diseases and problems accompanying renal failure, and selection of appropriate anesthetic technique for the operation [1-9].

For renal transplantation, most centers prefer general anesthetic techniques as they offer better hemodynamic stability, muscle relaxation, and foreseeable anesthetic depth. While in general, balanced anesthetics is preferred with volatile anesthetics along with opioids, there are other approaches, too [9].

Vandam et al. [10] aimed to avoid general anesthetic complications in uremic patients by defining the regional anesthetics use for renal transplantation. However, these do not present an important problem anymore with the presence of modern dialysis techniques [9]. Later, Linke and Merin [11] reported that regional anesthesia in renal transplantation patients had advantages such as not requiring neuromuscular medication and endotracheal intubation, decreasing the risk of regurgitation and pulmonary aspiration in all patients and providing a painless postoperative recovery.

Post-subarachnoid blockage analgesic effect begins faster in patients with chronic renal failure because the degree of metabolic acidosis ionization increases and the volume of the epidural cavity decreases with the dilatation of epidural and spinal veins due to hyperdynamic circulation. Sensory and motor blockage duration is shorter (20%) as a local anesthetic is removed away from the effect site more rapidly with increased cardiac output in such patients [12,13].

There is a risk of extradural hematoma in patients with coagulation disorders. It was first reported by Basta and Sloan [14] that epidural hematoma developed 60 hours after an epidural catheter had been inserted into a patient with renal failure. There are some disadvantages and complications such as difficulty in the management of large blood loss due to vasodilation, unexpected response to vasopressors in hypertensive kidney patients, maintaining the well-being of the patient who is awake during the long-term operation and neuropathy likely to develop postoperatively [9].

All volatile anesthetics reduce the mean arterial pressure depending on the dose. It has been shown that the administration of 1000 ml 0.9% sodium chloride solution provides a similar increase in arterial and central venous pressure regardless of the volatile anesthetic used [15,16]. It has also been shown that there is no effect on the postoperative renal function when halothane, enflurane and desflurane anesthesia were used in patients who underwent renal transplantation from live donors [17].

Patients with renal dysfunction may develop cardiac arrhythmia secondary to changes in plasma electrolyte concentrations. Acute hemodynamic changes due to the release of renin and catecholamines from the revascularized kidney during transplantation also increase the risk [18]. Ventricular arrhythmia may also develop due to endogenous catecholamines. Isoflurane and desflurane are the preferred agents in renal transplantation as they do not increase the sensitivity of myocardium to these amines [9].

There have been studies comparing epidural versus nitrous oxide-isoflurane anesthesia [19], isoflurane versus desflurane anesthesia [20], fentanyl-isoflurane versus propofol-alfentanil [21] or propofol-remifentanil total intravenous anesthesia [22] and combined spinal-epidural anesthesia [23] techniques. None of these anesthetic methods seem to affect the outcome of transplantation [9].

**General Anesthesia for Live Donors in Renal Transplantation**

Live donor nephrectomy can be performed using open or laparoscopic techniques. Today, the traditional open technique has been replaced almost entirely by the laparoscopic technique. Laparoscopic technique can also be divided into transperitoneal or retroperitoneal techniques. In the transperitoneal technique, as in other intraperitoneal laparoscopic surgeries, adverse effects on the cardiovascular system may occur due to carbon dioxide insufflation. Mechanical effects of pneumoperitoneum, neurohumoral responses, systemic absorption of carbon dioxide and mechanical effects of patient position are the factors that play a role. Pneumoperitoneum caused by carbon dioxide insufflation reduces renal blood flow [24], leading to intraoperative transient renal dysfunction. There are different views stating that this may lead to delayed graft function [25,26].

Electrocardiography, non-invasive blood pressure, pulse oximetry, end-tidal anesthetic and carbon dioxide values, body temperature and urine output should be monitored in the monitoring of laparoscopic nephrectomies. There are also advocates of central venous pressure measurement to ensure normovolemia and avoid renal perfusion disorder [9].

The anesthesia technique in these healthy patients does not differ from the one applied in other laparoscopic operations [8]. The use of nitrous oxide is contraindicated because it causes bowel distension and makes the surgery difficult [27].

The main objectives are to maintain intra-abdominal pressure below 12 mmHg, to establish positive fluid balance and to provide adequate urine output using mannitol and furosemide if necessary. To achieve good diuresis and optimize graft function, fluid is administered generally although blood loss is minimal in most cases (10-20 ml/kg/h). The type of fluid to be preferred first is ambiguous as there are not enough human studies to address this issue. Many medical centers use isotonic crystalloid fluids. Urine output should be supported with a diuresis target of 300-500 ml/h. While this goal is partially achieved by fluid loading, mannitol at a dose of 1-2 g/kg should also be used. Mannitol promotes urinary output as well as helping maintain renal function and protects the donor against cerebral edema secondary to increased cerebral blood flow. Furosemide may be added if necessary to achieve adequate diuresis. In an analysis evaluating possible renal protective strategies, it was argued that loop diuretics, mannitol, atrial natriuretic peptide analogues and dopamine infusion did not have positive effects, and the only beneficial preventive approach against renal damage was to provide adequate circulation volume and optimal renal blood flow [9,28].

Intravenous heparin (5000-5000 IU) is administered shortly
before the renal vessels are clamped. Protocols may vary between medical centers; close communication with the surgeon is essential [8]. Postoperative pain is usually mild to moderate and can be easily kept under control by intravenous opioids in the early postoperative period [8].

**General Anesthesia for Recipient in Renal Transplantation**

Benzodiazepines are generally used in premedication to relieve patients’ anxiety before transplantation. Since uremic patients are prone to coagulation disorders, intramuscular administration is avoided [9]. The risk of aspiration during anesthesia induction should be taken into account in patients who have uremia and comorbidity factors such as diabetes. Premedication with clear, particle-free antacid (such as 30 ml sodium citrate) increases gastric pH. Routine antacid prophylaxis is recommended for patients with reflux symptoms. Histamine H2-receptor antagonists (e.g., ranitidine) or proton pump inhibitors (e.g., omeprazole) may be administered in premedication to reduce gastric acidity. Phenothiazine-derived antiemetics and metoclopramide should be used with caution as they may cause prolonged sedation and extrapyramidal side effects in patients with renal failure [7,8].

Care should be taken to protect functional fistulas and shunts during surgery. The blood pressure cuff must be attached to the other arm. Vascular access should be limited to the peripheral veins as much as possible, all forearm and antecubital fossa vessels should be preserved, and the back of the dominant hand should be preferred for venous access [9]. Since the incidence of ischemic and hypertensive heart disease is high in transplantation patients, ECG and blood pressure monitoring in the perioperative and early postoperative periods should be continued during induction of anesthesia. For non-invasive blood pressure measurement, the blood pressure cuff should be attached to the non-fistula arm. Arterial cannulation is rarely needed in perioperative blood pressure monitoring because preoperative preparation of renal transplantation patients is well performed and excessive blood loss is observed exceptionally. Nevertheless, arterial blood pressure monitoring may be required in patients with concomitant advanced-stage comorbidity factor. Serious fluctuations in blood pressure may be observed in such patients. It was reported in a large case series that hypotension (49.6%) was more frequent than hypertension (26.8%). Patients with very severe comorbidities such as symptomatic coronary artery disease or congestive heart failure can be monitored for ischemia or severe hemodynamic disorders in the intraoperative period with pulmonary artery catheter or transoesophageal echocardiography. The aim of the preoperative blood pressure method is to maintain the blood pressure close to patient’s normal blood pressure values.

Patients with hypertension are under risk for large fluctuations in blood pressure and heart rate during anesthesia induction and endotracheal intubation. Since the prevalence of coronary artery disease and myocardial ischemia is higher in such patients, blood pressure and heart rate should be kept under control to minimize the risk of myocardial ischemia during induction. A few methods can be used in this case. An opioid such as fentanyl at a mid-to-high dose may mitigate the response to laryngoscopy; however, in this case, it is generally hard to control the blood pressure without using a vasoconstrictor after the induction. Remifentanil is a short-acting opioid metabolizing in the plasma and an effective drug for good heart rate control. As a short-acting beta adrenergic blocker, esmolol (0.5-1 mg/kg) is used to mitigate the hemodynamic response to intubation [8]. A few clinical studies have shown that the dose of propofol required to ensure clinical hypnosis and reduce the bispectral index (BIS) to 50 is 40% to 60% higher than the required dose for normal patients, in terms of induction doses of propofol. A negative relationship was found between the dose of propofol and preoperative hemoglobin level. Nevertheless, the mechanism is yet to be fully understood, and based on these findings, it is recommended not to administer a high induction dose [8,29,30].

For perioperative pain control, drugs such as morphine, meperidine or oxycodone should be used carefully in renal failure patients because these drugs or their active metabolites are removed renally and their accumulation may be observed in this patient group [31]. Fentanyl, sufentanil, alfentanil, and remifentanil are safe alternatives [8].

Central venous pressure (CVP) measurement is as important as blood pressure measurement in renal transplantation patients. The aim of the CVP monitoring is to keep CVP at 10-15 mmHg to optimize cardiac output and renal blood flow. A study showed that pulmonary artery pressure was correlated with graft function. High filling pressures (pulmonary artery pressure >20 mmHg/diastolic pulmonary artery pressure >15 mmHg) were found to be concluded with better graft function than low filling pressures [8]. In recent years, there have been controversies about whether a certain crystalloid fluid is better for postoperative renal function than others. An extensive survey study conducted in 49 hospitals in the US showed that normal saline or normal saline-based solutions were used during transplantation in more than 90% of the patients [32]. However, in a prospective, randomized, controlled and double-blind study comparing normal saline and Ringer’s lactate solution in intraoperative fluid management for renal transplantation, a higher rate of severe hyperkalemia and metabolic acidosis was observed in the normal saline group. Since blood loss in renal transplantation surgeries is minimal in general, transfusion is rarely required. In case of unexpected bleeding, transfusion can be performed with a hemoglobin concentration at approximately 10 g/dl [10].

Mannitol is usually administered to the donor before the graft is removed and to the recipient just before the arterial clamp is opened. Thus, mannitol can both protect against ischemic damage and induce osmotic diuresis in the newly transplanted kidney. In many medical centers, mannitol is administered in low doses (0.25-0.5 mg/kg) [8]. Hypotension may occur during reperfusion of the graft with the clamps opening in the iliac vessels. Severe hypotension periods should be avoided since renal graft function is based on adequate perfusion. It is believed that vasoconstrictors with strong α-adrenergic effects such as phenylephrine should be the last resort [10]. In several animal models, transplanted organ vessels were observed to be more susceptible to sympathomimetics, which compromised blood flow to the transplanted kidney [34,35].
Immediate urine output is seen in more than 90% of live donor renal transplants and 40% to 70% of cadaveric transplants. The decrease in urine output towards the end of surgical site closure suggests a mechanical problem in the grafts, vessels or ureter. A Foley catheter should be flushed to assess any blockage (e.g. clot, etc.). Intraoperative ultrasonography can be used to show flow in arterial and venous anastomoses. In addition to providing adequate intraoperative perfusion pressure, the use of mannitol, loop diuretics, and sometimes dopamine although evidence is controversial, increases urine output [8].

Assessment of hemoglobin and electrolytes during the operation has become more routine due to increased availability of in-surgery tests such as blood gas analysis [9]. Sudden increases in potassium have been reported to cause arrhythmia and cardiac arrest [36]. Various factors such as administration of mannitol or stored blood, severe metabolic acidosis, and hyperkalemia or hyperglycemia may be responsible [37,38]. Especially in diabetic patients, more attention should be paid in this regard. If urine output exceeds 300 mL/h, serum sodium and potassium values should be checked frequently. If urine output is more than 1000 mL/h, potassium supplementation (10 mmol/L) may be required. Excessive fluid loss may also lead to decreased intravascular and intracellular volume, resulting in tachycardia (ventricular tachycardia or atrial fibrillation) or attacks [9].

In diabetic renal transplantation patients, it is important to maintain normoglycemia through strict blood sugar monitoring during the perioperative period [9].

**Postoperative Care**

At the end of the operation, patients should be extubated and taken to the recovery room after ensuring that the muscle relaxant effect is fully reversed. Patients requiring mechanical ventilation should be admitted to the intensive care unit (ICU) [8, 9]. The incidence of hospitalization of renal transplantation patients in an ICU postoperatively was low in general and was found to be around 1% in a large series. The reason requiring admission to an ICU is usually sepsis or excessive fluid load [39]. An issue that anesthesiologists should be aware of and pay attention to is the interaction between neuromuscular drugs and cyclosporine. Sidi et al. [40] found the incidence of postoperative respiratory failure to be higher in the transplant patients using cyclosporine as an immunosuppressant. After extubation, all patients should be given oxygen for 12-24 hours [9].

Transplantation patients should be followed up in units where full monitoring and oxygen therapy can be performed postoperatively. The correct placement of the central venous catheter should be checked radiologically in the recovery room. It is very important to closely monitor the balance of liquid intake-output, and ECG, blood pressure, heart rate, central venous pressure, and oxygen saturation with pulse oximetry should also be monitored routinely [9].

While the postoperative fluid requirement depends on renal function in the early period, central venous pressure should be kept at the intraoperative level. Crystallloid (5% dextrose and Ringer’s lactate solution in equal amounts) is suitable for being used in fluid replacement and can be reinforced by colloids in cases where central venous pressure drops along with hypotension. When central venous pressure is sufficient (6-10 mmHg) but hypotension persists, a response to a vasoconstrictive agent such as noradrenaline is normally achieved. Assessment of fluid balance in the postoperative period may be difficult in patients with preoperative diuresis who do not undergo dialysis because kidney can respond to the high osmotic load of creatinine, urea and other solutes with urine output of up to 40 liters in the first 24 hours after transplantation from a live donor. Urine output returns to normal within 24-48 hours. Due to this excess fluid loss, the patient’s body temperature should be monitored throughout the operation. Heat balance must be maintained by heating the patient with the supplied fluids and convection heaters. A cause of massive diuresis is the initial diuretic phase of acute tubular necrosis characterized by excessive dilated urine output [9].

In patients with low urine output in the absence of dehydration, electrolytes should be checked every 6 hours and body weight should be checked every 24 hours. Dialysis is avoided in the first 24 hours postoperatively, but dialysis indication exists in the presence of massive weight gain, severe hypertension, pulmonary edema, severe metabolic acidosis or hyperkalemia [9]. Urine output should be strictly monitored. Any significant decrease in urine output should suggest that there may be a correctable mechanical problem in the transplanted kidney. Re-exploration of the surgical site should not be delayed if it is suspected that the veins are bent or there is obstruction during the course of the ureter or where it is reimplanted into the bladder [8].

**Postoperative Analgesia**

Postoperative pain after renal transplantation is usually mild to moderate [8]. Analgesia should be titrated according to the needs of the patients. Care must be taken in the selection of opioid and non-opioid drugs because active metabolites of pethidine and morphine may accumulate in patients with allograft non-functioning. Excessive opioid use can lead to delayed respiratory depression, sedation, and convulsions. PCA may help achieve a more effective and safe titration in ensuring the desired analgesic effect [9]. However, deep sedation and respiratory depression have been reported after PCA use in patients with end-stage renal failure [41]. Centers experienced in renal transplantation operations recommend the following doses for PCA administration in postoperative analgesia: 1-2 mg bolus dose of morphine, lockout interval of 5-10 minutes or 20 μg bolus dose of fentanyl, lockout interval of 5-6 minutes; and there is no basal infusion in either application [9]. Although only a few of the non-steroidal anti-inflammatory drugs (NSAIDs) are excreted in an unchanged state from the kidneys, there is evidence that renal clearance decreases in renal failure due to deconjugation of ketoprofen, fenoprofen, naproxen, and carprofen, possibly acyl glucuronide metabolites. NSAIDs can also cause reversible renal damage by reducing renal blood flow and glomerular filtration rate. They may also cause renal edema, interstitial nephritis, and papilla necrosis. It is highly likely that these effects are due to the effects of NSAID on prostaglandin synthesis, which is important in autoregulation of renal blood flow and glomerular filtration rate. These drugs should be avoided in transplanted patients and all patients with renal dysfunction [9].
One study showed that intraoperative anesthetic selection affected postoperative pain control. It was shown that the patients receiving propofol as a component of anesthesia had a better return of psychomotor functions and used patient-controlled analgesia more effectively than the patients receiving halothane or isoflurane [42]. It was shown that intercostal nerve blockage did not affect the use of patient-controlled analgesia or pain control after surgery [43].

Anesthesia for renal transplantation

Anesthesia-Related Complications After Renal Transplantation

Major postoperative anesthesia complications include vomiting and pulmonary aspiration, arrhythmia that may lead to cardiac arrest, pulmonary edema, hypotension, hypertension and delayed respiratory depression. Cardiovascular complications account for approximately 33% of mortality in transplant recipients [44]. Approximately 50% of patients have arterial hypertension. Hypertension is usually due to chronic rejection or excessive renin release from the patient's own kidney. Immunosuppressive drugs (especially cyclosporine), recurrent glomerulonephritis and transplanted renal artery stenosis are other rare causes of hypertension [9]. Furthermore, the risk of developing left ventricular hypertrophy was found to be higher in transplant patients who required two or more antihypertensive drugs for blood pressure control [45].

Diabetes mellitus occurs in 3% to 16% of recipients after transplantation, and approximately 4% of them require insulin therapy. Hyperglycemia usually begins within the first three months of transplantation or after the administration of a single dose of bolus steroid used for rejection therapy. Preoperative glucose intolerance and presence of HLA B28 are predisposing factors [9].

Increased awareness of existing surgical risk factors in renal transplantation patients along with careful peripereoperative follow-up and monitoring have led to a decrease in perioperative mortality rates (0.03% - 0.06%). Factors increasing perioperative risk in renal transplantation patients include the recipient age of over 60 years, coronary artery disease and diabetes mellitus [46].

Actions to Be Taken for Early Allograft Function

Loop diuretics and manitol can be used to increase diuresis in the kidney.

Mannitol increases intravascular volume by drawing extravasated fluid into the vessel. It passes freely through the kidney glomeruli, not being reabsorbed from the distal tubules. Due to its osmotic effect, sodium and water are excreted together, which may lead to an increase of 0.7 mmol/L in serum potassium level. Although the use of manitol has been criticized, there is evidence that it may have a protective role as a free radical scavenger that prevents free radical-induced reperfusion injury [9]. Mannitol reduces the incidence of post-transplantation renal dysfunction from 55% to 14% [47]. It has also been shown to increase renal blood flow at a higher rate than plasma volume expander alone [48]. It has been shown that delayed graft function in the cadaveric kidneys can be prevented by intraoperative manitol administration [49].

Moote and Manninen [50] investigated the effects of manitol on serum electrolytes in renal transplantation patients. It was found that 50 g manitol increased central venous pressure and decreased serum sodium, chloride, and bicarbonate concentrations. The increase in potassium is small, but it may be important in patients also undergoing blood transfusion. Blocking the Na+/K+ pump in the emerging thin arm of the Henle handle, loop diuretics manifests its effect by blocking the electrolyte reabsorption in this segment of nephron. This high-osmolar fluid prevents the reabsorption of water in the distal tubule and causes large volumes of urine output with high electrolyte content. While the main effect of loop diuretics is increasing urine output, its ability to prevent oliguria (400 ml/day) can be a significant success [10].

It is also important to maintain adequate circulation volume in combination with the use of mannitol and other diuretics to induce diuresis. When using thiazide diuretics and furosemides, it is recommended that patients be loaded with 0.9% sodium chloride solution beforehand. Davidson et al. [51] reported that urine output was delayed after reperfusion in patients with blood volume less than 70 mL/kg. Hydration requirement can be predicted depending on the central venous pressure, and normal saline is initially preferred as volume expander. Colloid solutions should be added if more than 40 to 90 mL/kg is thought to be required. Fluid loading also creates a physiological stimulus for urine output. This stimulus is important because many analgesics and inhalation anesthetics increase the level of circulating antiuretic hormone [52].

“Renal dose” or low-dose dopamine (2-3 μg/kg/min) has been widely used to stimulate DA1 dopaminergic receptors to induce vasodilation and increase urine output. While some small-scale studies [53] have shown that low-dose dopamine improves urine output and creatinine clearance during renal transplantation, other large-scale studies [54,55] have shown no significant improvement. The benefit of this approach has been questioned as a newly transplanted, denervated kidney may not respond to low-dose dopamine like a normal kidney. Doppler ultrasonography assessment of newly transplanted kidneys showed that dopamine infusion of 1-5 μg/kg/min did not cause any significant change in blood flow [56]. Consequently, we think that the anesthesia technique, the choice of drugs, fluids and analgesics administered as well as the pre-and post-anesthetic care and preparation of the patients are effective in the success of renal transplantation and that the up-to-date information on the practices should be implemented.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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