Kidney transplantation: recent developments and recommendations for anesthetic management

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For patients with end-stage renal disease (ESRD), a transplant provides better survival and quality of life than dialysis [1–5]. After transplantation, the 5-year survival is approximately 70%, and 5-year survival is only 30% for a similar group of patients receiving dialysis (Fig. 1). Following successful renal transplantation, serious comorbidities associated with ESRD, such as cardiomyopathy, may resolve partially or even completely [6].

In the first reports of the 1960s [7,8] describing anesthetic management of patients undergoing kidney transplantation, perioperative mortality and morbidity were high. Problems encountered by anesthesia providers included severe anemia, hypertension, metabolic acidosis, congestive heart failure, hyperkalemia, hyponatremia, and circulatory collapse. Advances in patient management and better preparation of patients for surgery and anesthesia led to dramatic improvements. By the mid 1990s, only 8 of 23,546 (0.03%) kidney transplant recipients recorded in the United States’ renal data system died on the day of transplantation [9]. Improvements in our understanding of ESRD and patient care, however, have resulted in an increasing trend toward transplanting higher acuity, older patients. The impact of this trend on perioperative morbidity and mortality is not clear.

Ideally, renal transplantation should precede the need for dialysis [4,10]. The success of transplantation is negatively affected by lengthy pretransplantation dialysis dependence [4]. Early transplantation to enhance chances of long-term survival, however, can only be achieved with living donor transplants. As of late January 2004, the deceased donor kidney (DDK) (a term preferred to the more familiar “cadaveric donor kidney” by the Association of Organ Procurement Organizations) transplant waiting list included approximately 59,500 registrants.
The number of DDK donations is approximately 9000 per year and is not expected to increase significantly. With the current system, in most regions in the United States 2 points are allocated for HLA-D-related matching, and 1 point is allocated for each year on the list; only patients on the top 2 years of the list are likely to receive a transplant. Because it is not possible to predict when those patients will be offered a DDK, transplant centers are required to maintain all patients in this group in optimal medical condition to decrease the chance of last-minute reconsideration or cancellation, or proceeding at higher recipient risk. Additionally, seeking a second recipient increases cold ischemia time. This review focuses on issues relevant to the practice of anesthesia in patients with ESRD.

Preoperative considerations and patient evaluation

Significant comorbidities that often afflict those with ESRD affect preoperative assessment, intraoperative management, and the immediate postoperative course of patients presenting for kidney transplantation. Diabetes is currently the most common cause of ESRD, and hypertension is the second most common cause. The prevalence of diabetic nephropathy has doubled in the past 10 years (Fig. 2). In the past, diabetic patients tended to be excluded from transplant candidacy because of the presence of other diabetes-related complications such as severe atherosclerosis and severe coronary artery disease.
Cardiovascular disease in patients with ESRD accounts for more than 50% of the deaths in this group [13]. Chronic renal failure itself is associated with hypertension, dyslipidemia, hyperphosphatemia, and hyperhomocysteinemia [14–16]. The short-term and long-term prognoses in patients with ESRD after myocardial infarction is poor; 40% of patients die of cardiac causes by 1 year, and almost 60% die by year 5 [17]. In young adults (aged 19–39 years) with childhood onset renal failure, the prevalence of advanced coronary and carotid artery disease is as great as 92% and is associated with indicators of microinflammation, hyperparathyroidism, calcium-phosphate overload, and hyperhomocysteinemia but not traditional atherogenic risk factors [18]. In another study [19] of young patients cardiovascular mortality was found to increase 700-fold and more than 10-fold after renal transplantation. The acute-phase C-reactive protein is chronically increased in 33% to 66% of dialysis patients [15]. This protein is considered a surrogate marker of a microinflammatory state and is a powerful predictor of cardiovascular mortality in both the general and ESRD population [15,16].

Exercise tolerance testing is currently recommended for patients with diabetes and for patients older than 50 [20]. Patients with reversible ischemia should undergo coronary angiography for possible correction of significant lesions; however, the decision to perform cardiac catheterization should not exclusively depend on the results of the stress test. The sensitivity and specificity of stress tests are relatively low, highly variable between studies, and the results may not be predictive of perioperative risk [21,22]. In a recent meta-analysis in patients
being evaluated for kidney or kidney-pancreas transplantation, the prognostic
value of myocardial perfusion studies was assessed (using multi-year follow up).
The sensitivity of myocardial perfusion studies was 0.8 for cardiac death and 0.7
for (nonfatal) myocardial infarction (MI) [23]. The specificity was 0.59 for both
cardiac death and MI. When compared with a negative stress test, a positive stress
test did have a significantly increased relative risk of MI (2.73) and cardiac death
(2.92). In diabetic patients, the relative risk of MI was 2.68 and 3.95 for cardiac
death when compared with a negative test. Subgroup analysis showed that re-
sversible defects were associated with increases in MI and cardiac death. Fixed
defects were associated with an increase risk of cardiac death but not MI.

A surprisingly high incidence (40%) of unexplained pulmonary hypertension
in patients receiving long-term hemodialysis through an arteriovenous fistula,
which could not be demonstrated in a control group receiving peritoneal dialysis,
has recently been reported [24]. After renal transplantation, pulmonary pressures
decreased to normal in the majority of patients.

Numerous hemostatic abnormalities have been associated with chronic renal
disease [25]. Abnormalities include abnormal platelet function and ineffective
production of both factor VIII and von Willebrand factor. Cryoprecipitate
and desmopressin (DDAVP) may have value for temporary treatment. Preopera-
tive dialysis improves platelet function and is the mainstay of the prevention of
uremic bleeding. In addition, a hypercoagulable state has been associated with
changes in hemostatic plasma protein factors such as lupus anticoagulant,
anticardiolipin antibody IgG and IgM, and deficiencies in protein S, protein C,
and antithrombin III [26–31]. After renal transplantation, plasma protein factors
associated with hypercoagulability become normal within 9 months [26].

Hepatitis C and chronic renal disease are linked in several important ways
[32]. Chronic infection with hepatitis C virus (HCV) can lead to the immune
complex syndromes of cryoglobulinemia and membranoproliferative glomerulo-
nephritis [33–40]. Patients with renal disease are at increased risk for acquiring
hepatitis C because of frequent transfusions and exposure to HCV-contaminated
dialysis equipment. In the United States, 8% to 10% of hemodialysis patients
demonstrate an anti-HCV response, and the incidence of new cases in patients re-
ceiving dialysis ranges from less than 1% to 3% [41–43]. Prevention of acqui-
sition is particularly important in these patients because HCV infection is
associated with significant worsening of survival in those undergoing dialysis
therapy and after renal transplantation [43–45].

Anemia has long been a problem in those with ESRD. The use of erythro-
poietin has resulted in a reduction of blood transfusions, and has improved
quality of life, cognitive function, exercise tolerance, cardiac function, and, most
importantly, survival [46].

Hyperkalemia is a common feature of chronic renal insufficiency and may be
an adaptive response that reflects a new set point for potassium hemostasis and
excretion [47]. Recognition that mild to moderate hyperkalemia is an adaptive
response should lead to tolerance of steady-state serum potassium levels of 5.0 to
5.5 mmol/L. Higher levels or acute increases must be treated.
Pharmacokinetics and pharmacodynamics

Chronic renal disease should not be considered an isolated event that affects only drugs excreted by the kidney. Chronic renal disease may also modify the disposition of drugs through changes in plasma protein binding or hepatic metabolism. For example, if total (free plus protein-bound) plasma concentrations are considered, many lipophilic drugs such as diazepam, midazolam, and thiopental appear to have an increased drug distribution and clearance. This is because of an increase in free fraction of the drug caused by diminished plasma protein binding; but if the pharmacokinetics are calculated in terms of free unbound drug, both distribution and clearance remain unchanged [48–50]. The net result is an underlying rate and extent of distribution and elimination much the same as in normal patients. The pharmacokinetics and pharmacodynamics of propofol are unchanged by chronic kidney disease [51].

Within 3 to 5 minutes after administration of succinylcholine, an increase in potassium of approximately 0.5 to 1.0 mEq/L occurs that lasts less than 10 to 15 minutes; however, succinylcholine can be used safely in patients with chronic renal failure, assuming that the potassium concentration is less than 5.5 mEq/L [52]. The duration of action of vecuronium and rocuronium may be prolonged [53–56]. The decreased clearance of rocuronium in renal failure patients is offset to some degree by an increase in the distribution volume [55,56]. Cisatracurium undergoes Hofmann elimination, an organ-independent elimination pathway occurring in plasma and tissue, which is not altered in patients with chronic kidney disease. The effect of mivacurium is prolonged by approximately 50% in patients with renal failure [57]. The long-acting muscle relaxant pancuronium is not suitable for use in patients undergoing kidney transplantation because of the kinetics of distribution and elimination. The kidneys excrete the majority of pancuronium and its active metabolite. For all muscle relaxants, the reported recovery times from neuromuscular blockade are highly variable in renal failure patients, and careful monitoring of the degree of neuromuscular blockade is recommended.

The pharmacokinetics and pharmacodynamics of fentanyl, alfentanil, sufentanil, and remifentanil are not significantly altered by kidney disease and can be used without modifying the dose [58–60]. The use of large doses or prolonged administration of meperidine and morphine is of concern in renal failure patients. Normeperidine, the active metabolite of meperidine, accumulates in patients with renal failure and may cause seizures [61]. Morphine-6-β-glucuronide, a metabolite of morphine with potent opioid agonist activity, is also excreted by the kidney and accumulates in renal failure patients. Because morphine-6-β-glucuronide passes the blood–brain barrier very slowly, insidious and long lasting opioid effects may occur after prolonged morphine administration [62]. In addition, meperidine and morphine cause histamine release, which may result in hypotension and hemodynamic instability, whereas fentanyl, sufentanil, alfentanil, and remifentanil are not associated with significant histamine release.
The safety of sevoflurane in patients with impaired renal function has been widely studied and debated [63–66]. Sevoflurane is metabolized by the liver to hexa-fluoro-isopropanol and inorganic fluoride. With methoxyflurane, a measurable toxic effect on renal function was detected after peak serum inorganic fluoride concentrations greater than 50 μmol/L [67] but not with sevoflurane [68]. This difference is probably because of the fact that with methoxyflurane peak fluoride concentrations remain increased for a longer duration than with sevoflurane. In another study [69], however, two of three patients with fluoride concentrations greater than 50 μmol/L after sevoflurane administration demonstrated increased serum urea nitrogen and creatinine levels at 24 hours. In patients with chronically impaired renal function, peak serum inorganic fluoride concentrations were significantly greater after sevoflurane than after enflurane anesthesia (25 ± 2.2 μmol/L versus 13.3 ± 1.1 μmol/L, mean ± SE), but no permanent deterioration of pre-existing renal insufficiency was observed [66]. Sevoflurane is degraded to compound A by carbon dioxide absorbers containing a strong base such as barium hydroxide lime or to a lesser extent by soda lime. Reductions in fresh gas flow as well as an increase in temperature in the gas mixture will increase compound A concentrations. Compound A has been shown to be nephrotoxic in rats, inducing dose-dependent corticomedullary renal necrosis [70–72]. In humans, albuminuria, glucosuria, and enzymuria are associated with inhaled doses of compound A greater than 160 ppm/hr [73–76]. Other studies have shown no adverse effects of compound A [77–83]. In the few studies in patients with renal impairment no evidence of further worsening of renal function could be demonstrated [64–66]. Renal function has been assessed by measurement of serum urea nitrogen and creatinine concentrations and creatinine clearance or by the measurement of the urinary excretion of sensitive markers such as protein, glucose, and N-acetyl-b-glucosaminidase or α-glutathione-S-transferase. The validity of such sensitive markers as reliable indicators of clinically significant renal injury has not been established. In rats, tubular necrosis appears at smaller doses of compound A than that associated with increases in serum creatinine [70–73, 75]. The safety of sevoflurane in patients with impaired renal function is unclear.

Desflurane biodegradation does not increase fluoride concentration. No evidence of deterioration in renal function has been noted in patients with or without renal disease [73,81,84,85]. Similarly, isoflurane has no nephrotoxic properties.

Anesthesia management

Adequate venous access should be established because there is a potential for rapid blood loss. Anesthesia monitoring should reflect relevant comorbidities and volume status that can vary with the time since the last dialysis. A central venous line aids in the assessment of volume status. Intra-arterial pressure monitoring
may prove useful, especially in patients with significant cardiovascular or lung disease or poorly controlled hypertension. The use of a pulmonary artery pressure catheter is seldom required but may be indicated for patients with severe coronary artery disease, left ventricle dysfunction, valvular abnormalities, or known pulmonary hypertension. Medications used for anesthesia induction should be titrated to minimize the possibility of hemodynamic instability. If the patient is at risk for aspiration, a rapid sequence type of anesthesia induction should be performed.

Intra-operative volume expansion is associated with increased renal blood flow and an improvement in immediate graft function [86–90]. Immediate function is associated with increased graft survival and lower patient mortality [91]. Central venous pressure is usually maintained in the range of 10 to 15 mm Hg to achieve this goal. Diuretics (furosemide), osmotic agents (mannitol), and sometimes dopamine agonists (dopamine, fenoldopam) are administered to promote diuresis immediately after reperfusion, but only mannitol, when combined with volume expansion, has been shown to decrease the incidence of acute tubular necrosis after transplantation [92,93]. Hypotension results in decreased graft perfusion. Maintaining an adequate intravascular volume and careful titration of medications are important. Keep in mind that vasopressors, especially alpha agonists, may interfere with renal perfusion.

In dual kidney transplantation, two kidneys from an aged donor are placed into one recipient. Such kidneys have usually been refused for single kidney transplantation. The graft survival in patients receiving a dual-kidney transplant is similar to the graft survival of single kidneys [94]. Other than the long duration of the procedure, there is no difference in anesthesia management.

In limited series [95], epidural analgesia has been effective in managing postoperative pain and is without significant complications. Many uremic patients have at least subtle coagulation defects. In the transplantation setting, these patients will receive heparin intraoperatively and occasionally into the postoperative period or for postoperative dialysis. Epidural anesthesia may complicate hemodynamic issues and perioperative fluid requirements and pose a risk for epidural hematoma.

Intravenous opioid administration provides the mainstay of analgesia following renal transplantation. Patient-controlled analgesia with fentanyl or morphine is widely accepted as an effective postoperative analgesic technique [96]; however, the possibility of significant accumulation of the potent morphine metabolite morphine-6-β-glucuronide makes fentanyl a safe and rational alternative [62].

Cardiovascular events are the most common cause of death after renal transplantation [97]. Even after comprehensive pretransplant evaluation, 6% of patients with coronary artery disease experience a cardiac complication within 30 days of the transplant procedure [98]. In diabetics, maintaining the hematocrit at greater than 30% is associated with a 24% reduction in cardiac risk in the first 6 months after transplant [99].

In summary, kidney transplantation is the treatment of choice for patients with ESRD. Successful transplantation increases survival and may resolve significant
comorbidities. In the future, more patients with significant cardiovascular disease and advanced age will present for transplantation. This review highlights commonly encountered issues in the perioperative anesthetic management of this increasingly complex group of patients.

References


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