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Intraoperative Management of the Kidney Transplant Recipient

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Abstract
Purpose of Review The purpose of this study was to review current literature on the intraoperative management of the kidney transplant recipient in terms of preoperative evaluation, anesthetic agents of choice, monitoring needs, intraoperative fluid and hemodynamic management, and perioperative pain control options.
Recent Findings More recent literature regarding intraoperative kidney management suggests less aggressive volume loading with a balanced crystalloid solution, particularly in regard to albumin and blood products, with increased consideration for multimodal therapies for nausea and pain control.
Summary Perioperative kidney management is crucial to immediate- and long-term outcomes for graft and patient survival. Surgical and anesthetic techniques should continue to be honed to allow for ideal renal perfusion intraoperatively. Considerations for intraoperative optimization for renal transplantation include the appropriate types and volume of fluid based on cardiac risk factors with the increasing number of elderly recipients, the avoidance of vasoconstrictive agents, and a reduction in perioperative cardiac-depressing agents for pain that may be managed by multimodal therapies.

This article is part of the Topical Collection on *Kidney Transplantation*

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Introduction

As the prevalence of end-stage renal disease (ESRD) continues to increase, so too has the need for kidney transplantation, which improves survival and quality of life while decreasing healthcare costs compared to dialysis [1–4]. Long-term outcomes of kidney transplantation also continue to improve as immunosuppression options have advanced. However, the ESRD population is aging and presents for kidney transplantation with significant comorbidities, including diabetes and cardiovascular disease, which must be evaluated preoperatively [5]. Additionally, it is recognized that early graft function influences long-term patient and graft survival and that meticulous attention to the perioperative period may optimize outcomes for all patients and particularly for those who are at increased risk for early adverse events [6].

Preoperative Evaluation and Premedications

Patients presenting for kidney transplantation have usually undergone extensive pretransplant evaluation by their transplant center. Since diabetes and hypertension are the most common etiologies of ESRD and these diseases as well as the uremic milieu contribute to the development of cardiovascular disease [7, 8], it is essential to understand these patients' burden of cardiac disease. Almost half of all perioperative mortalities in the first 30 days after transplantation are from cardiac causes [9]. Although there are existing guidelines for pretransplantation cardiac screening, these recommendations are often based on

observational data and are inconsistent with existing, large randomized controlled trials in nontransplant patients which do not show benefits of preoperative revascularization in terms of adverse cardiac events or mortality [10–12]. For transplant patients with symptomatic cardiac disease or who are high risk by having at least two of the following factors: hypertension, diabetes, hyperlipidemia, obesity, tobacco use, prior ischemic heart disease, males age >45, females age >55, a first-degree relative with a history of ischemic heart disease, or evidence of left ventricular hypertrophy, it is reasonable to perform a noninvasive test such as a dobutamine stress echocardiogram or nuclear myocardial perfusion study. Rabbat et al. in 2003 [13] showed a significant association between positive noninvasive testing and worse outcomes for kidney transplant candidates; however, subsequent studies have shown no association [14, 15]. Those individuals with diminished ejection fractions below 35–40% or signs of ischemia on stress testing are usually referred for cardiac catheterization and subsequent intervention such as coronary artery bypass grafting (CABG) or percutaneous cardiac stenting (PCI) as Manske et al. showed significantly decreased perioperative cardiac morbidity and mortality for those diabetic patients who were revascularized versus those who were not [16]. Our center's evaluation policy stratifies by cardiac risk with increased consideration for those with diabetes. We prefer dobutamine stress echocardiography based on its ability to incrementally risk stratify diabetics with an acceptable predictive value for ESRD patients while being less expensive than a nuclear perfusion study [17, 18]. Revascularization via either PCI or CABG is recommended for those patients who have significant stenosis on cardiac catheterization. We feel this has been an acceptable approach as a recent evaluation of our 30-day posttransplant perioperative risk for cardiac complications was 4.1%, less than the 6.1% suggested by previous studies [19].

Kidney transplant recipients have significant comorbidities such as hypertension, volume overload, electrolyte and metabolic disturbances, diabetes with concomitant glucose control and gastroparesis concerns, and pulmonary impairment. Up to 70% of patients presenting for transplantation have preexisting hypertension. Perioperative management of their hypertension should involve use of baseline anti-hypertensives with the exception of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, which decrease renal blood flow and may exacerbate acute tubular necrosis. Additionally, they may cause refractory hypotension during general anesthesia [20]. Perioperative beta-blockers should be continued to decrease the incidence of rebound tachycardia and risks of cardiac ischemia [21]. Additionally, it is recommended that patients should undergo dialysis within 24 h of kidney transplantation to allow for optimal volume and electrolyte status, which may also allow for decreased postoperative dialysis in the setting of slow return of allograft function [22]. Preoperative and intraoperative glucose testing should be routine for diabetic patients especially since induction of immunosuppression with steroids may precipitate hyperglycemia. Hyperglycemia is associated with increased risk of surgical site infection and cardiac morbidity in the perioperative period [23]. Patients should continue any therapy such as proton pump inhibitors or histamine$_2$ receptor blockers as they would at home. Metoclopramide 10 mg intravenous (IV) given 30 min before surgery has been associated with improved gastric emptying for those with known gastroparesis [22]. In an effort to decrease intraoperative narcotic requirements, associated postoperative nausea and vomiting (PONV), and ileus development, acetaminophen is administered preoperatively [24]. Although many laboratory tests including viral serologies, prostate tumor markers, and hypercoagulable state evaluations may have been ordered in waitlist evaluation visits, immediate preoperative laboratory testing at our center includes a complete blood count, comprehensive metabolic panel, coagulation factors, blood type, type and screen, and a pregnancy test for reproductive-aged women. A preoperative ECG and chest x-ray are also performed. Prophylactic antibiotics are given within 30 min of incision, and cefazolin is the standard [25]. Preoperative heparin 5000 units subcutaneous and sequential compression devices are also used for deep venous thrombosis prophylaxis. Induction agents such as alemtuzumab, basiliximab, or antithymocyte globulin (rabbit) (ATG) may be given with methylprednisolone at or after induction.

Intraoperative Positioning, Procedure, and Monitoring

Patients are in the supine position during kidney transplantation. We often utilize a kidney rest in the operating room table to elevate and extend the pelvis to allow for decreased angulation of the external iliac vessels. Both arms are extended with enough space to allow for the posting bar for a self-retaining retractor. As many ESRD patients have functioning vascular access sites for hemodialysis, careful attention to positioning and padding of these extremities is crucial to their ongoing function. A curvilinear lower quadrant incision on the side of kidney transplant implantation is usually performed with a midline incision employed for those with multiple prior transplants or vascular concerns. The operation involves arterial and venous clamping of the recipient artery and vein of choice, which is usually the external iliac artery and vein; however, the common iliac vessels, aorta, or vena cava may be involved. Clamp time, or warm ischemia time for the anastomosis, on average is 30–40 min, and prolonged anastomotic times have been shown to negatively correlate with both immediate and longer-term allograft function [26]. Once the vascular anastomoses are performed, the ureter is anastomosed to the bladder with or without ureteral stent placement per transplant center protocol. The operative length is about 2–3 h.

As far as intraoperative monitoring, this varies depending on institution and patient factors, although the American Society of Anesthesiologists (ASA) guidelines for major surgery are

usually incorporated and include pulse oximetry with capnography, ECG leads, blood pressure monitoring, adequate peripheral venous access, and neuromuscular relaxation monitoring [27]. Invasive monitoring with an arterial line may be reserved for those with cardiac risk factors such as severe coronary artery disease, poorly controlled hypertension, low ejection fraction, or valvular heart disease [28]. Some centers may place invasive central venous catheters in patients for induction agent infusion such as with ATG, for venous pressure measurements for volume status, and/or to assist with frequent blood draws in patients with difficult IV access. Transesophageal echocardiography (TEE) may be considered in patients for continuous evaluation of ventricular function and pulmonary artery pressures in those with known ventricular dysfunction, valvular heart disease, or pulmonary hypertension. Pulmonary artery catheters (PAC) are rarely used and have not been shown to improve outcomes [29]. Since our center gives one dose of alemtuzumab for immunosuppression induction during the operation, central venous lines are placed only if IV access is tenuous or if it is felt that increased intravascular monitoring or ability to infuse volume is warranted. Arterial lines are also only placed for those having specific criteria. We do allow the use of tunneled dialysis catheters for IV access if a suitable peripheral IV cannot be obtained.

Anesthetic Agents of Choice

Although general anesthesia (GA) is usually performed for renal transplantation at most centers, neuraxial anesthesia whether epidural, spinal, or combined spinal epidural was the initial anesthetic of choice for transplants with renewed interest more recently as some centers have reported their experiences with good outcomes with this technique. Epidural anesthesia (EA) has been associated with improved cardiovascular stability, decreased blood loss, and improved pain control [30–32]. In one randomized study comparing combined spinal epidural or general anesthesia for kidney transplant surgery, there was no difference in anesthesia time, surgical time, heart rate, systolic blood pressures at all points measured, bradycardia, or hypotension, showing it to be a reasonable alternative to GA [33].

GA with endotracheal intubation is generally performed for kidney transplantation with volatile anesthetic maintenance. If patients have significant PONV or other considerations, total IV anesthesia (TIVA) with propofol preceded by fentanyl has been shown to be a suitable alternative with similar pharmacokinetics and hemodynamics to inhaled anesthetics [34]. Induction may be performed via rapid sequence if the patient has a known history of poorly controlled diabetes or risk factors for increased gastric contents in order to minimize aspiration. We induce with a short-acting hypnotic, such as propofol, as well as medications to blunt the tachycardic response to laryngoscopy and intubation such as fentanyl and lidocaine. Fentanyl is not only short-acting but minimally cleared by the kidney (7%) [28]. A neuromuscular blocking agent (NMBA) is administered as well and for induction is usually rocuronium or vecuronium. The former has a short latency, is hepatically cleared, and is not altered by renal dysfunction. Succinylcholine may be used for induction if the potassium level is <5.0 mmol/L [35]. Prior to proceeding to the operating room, a short-acting anxiolytic such as midazolam may be considered. Maintenance anesthesia is provided by a volatile anesthetic, isoflurane, which can be in an air/oxygen mixture or combined with nitrous oxide, which decreases the amount of inhalational agent needed and may decrease myocardial depression [29]. Inhalational agents are supplemented during the maintenance phase with short-acting narcotics such as fentanyl. If concerns about PONV or postoperative pain control are of particular concern, other medications such as lidocaine or ketamine infusions may be used intraoperatively. NMBA are administered throughout the case to avoid movement until the fascial closure. Cisatracurium, which does not rely on renal elimination and undergoes ester hydrolysis via Hofman degradation, is usually used for maintenance NMBA [28].

Fluid Management

Some kidney transplant recipients may come to the operating room hypovolemic due to recent dialysis and lack of oral intake. Several induction agents and volatile inhalational agents can decrease systemic vascular resistance (SVR) and in the setting of decreased circulatory volume may lead to hypotension. Although controversies exist in the literature regarding the extent of volume loading and type of fluid to use, it is clear that intraoperative volume expansion is needed to increase renal blood flow after reperfusion and avoidance of hypotension, ideally without pressor support, is paramount. Kidney transplant graft and patient survival outcomes have been correlated with perioperative renal function, such as early urine output and diuresis [36, 37].

Initial studies in fluid loading established the standard for maximal hydration intraoperatively. One study by Luciani et al. reported on 100 consecutive kidney transplant patients who were administered large fluid volumes directed by pulmonary arterial pressure (PAP). The average intraoperative fluid loads were approximately 2.4 L of water with 22.8 g of sodium chloride, 5.9 units of albumin, and 2.5 units of packed red blood cells (prbcs). Postoperatively, the patients remained ventilated and fluid administration matched diuresis if at or above 400 mL/h. If diuresis was not at this level, additional saline, albumin, and prbcs were administered with furosemide being utilized to promote diuresis if fluid loading failed to achieve this level of urine output. They found that 95% of patients achieved this high-output early diuresis with a decreased mortality rate and an increased graft survival rate [38]. Maximal hydration utilizing PAPs was also

associated with improved allograft function when studied by Carlier et al. They divided two groups of 120 patients into those with PAPs ≤20 mmHg and diastolic PAPs ≤15 mmHg at reperfusion and those with PAPs >20 mmHg and diastolic PAPs >15 mmHg. They found that the frequency of acute tubular necrosis (ATN) was 36% in the lower PAP group vs. 6% in the higher PAP group at the time of vascular unclamp, concluding the importance of intravascular volume at the time of reperfusion [39•]. Timing of volume loading has also been evaluated by comparing a constant infusion rate during the time of induction to case completion vs. volume loading during the time of vascular anastomosis, and the latter may enhance early graft function [40].

These studies have led to a recommendation of CVP between 10 and 15 mmHg to ensure adequate volume expansion at the time of reperfusion. However, with the increasing number of patients with cardiac comorbidities, aggressive fluid management has been questioned and more recent findings suggest that a more conservative fluid policy (crystalloid average of 2.4 L with a CVP range of 7–9 mmHg) was associated with good allograft recovery and function [41•]. We do not routinely place central venous lines, but do utilize approximately 2.5–3.5 L of crystalloid per transplant, which is approximately 15 mL/kg/h. Volume infusion is titrated to hemodynamic measures such as blood pressure and heart rate.

The constituency of the appropriate fluids to administer has also been recently debated. Traditionally, crystalloid infusion with normal saline has been utilized by the majority of centers; a survey in 2002 showed 94% of centers used 0.9% normal saline (NS) [42]. Subsequently, this same group, O'Malley et al., showed that hyperkalemia and metabolic acidosis were significantly greater in patients who received normal saline compared to those who received lactated Ringer's solution (LR), although the NS group did not have worse renal function [43]. A more recent study compared the use of an acetate-buffered balanced crystalloid solution (e.g., Plasmalyte-A, Normosol-R) versus NS and found increased hyperchloremia and need for catecholamine administration for circulatory support in the NS group, although there was no difference in creatinine or urine output postoperatively [44]. Hadimioglu et al. compared NS, LR, and Plasmalyte and found that all are safe options, but physiologic parameters are most maintained in the patients who received Plasmalyte [45•]. These recent studies have altered our crystalloid choice, which intraoperatively is now Plasmalyte.

Colloids, such as albumin, have been shown in a dose-related manner (1.2–1.6 g/kg bodyweight for a high dose group vs. 0–0.4 g/kg bodyweight for a low dose group) to improve rates of delayed graft function, glomerular filtration rate, and graft and patient survival presumably through volume expansion, minimization of hypoxic injury, and preservation of renal tissue [46]. However, the use of colloids has been questioned as multiple trials do not demonstrate benefits of albumin use over crystalloids [47, 48], and one large cohort study suggests that albumin is associated with increased risk of acute renal failure [49]. Blood products are given in the setting of ongoing blood loss and transfusion trigger guidelines of a hemoglobin <7 or <8 g/dL in those with known cardiac disease as several studies have shown improved outcomes including for mortality with a restrictive transfusion strategy [50, 51].

Diuretics have been given during kidney transplantation to promote diuresis at the time of reperfusion. The administration of mannitol with moderate hydration has been shown to reduce ATN from rates as high as 42% to less than 5% [52]; the mechanism for this reduction is thought to be from mannitol's osmotic effect on the nephron to increase renal volume and its protective effect on renal tubule ischemia [28]. Furosemide blocks the sodium-potassium-chloride pump in the thick ascending limb of the loop of Henle and, in promoting diuresis, can aid in preventing oliguric renal failure [28]. Although one study demonstrated no difference in immediate graft function or 1-year graft outcomes with or without diuretic use [53], our practice has been to administer both immediately after unclamping of the newly anastomosed vessels.

Hemodynamic Management

The goal is to have adequate perfusion pressure at the time of vascular unclamping and reperfusion of the kidney. We target a mean arterial pressure of 70 to 90 mmHg, preferably with volume expansion, with judicious use of anesthetic or immunosuppressive induction agents and inhaled anesthetics, and without the routine use of vasopressors. Alpha-agonists such as phenylephrine should be avoided due to the risk of vasoconstriction in the renal allograft, which can impair outcomes with reduced renal blood flow [54]. Low-dose dopamine to increase renal blood flow was evaluated and does not improve renal function and was associated with increased heart rate, length of ICU stay, and 6-month mortality [55•]. Dopamine may be considered for its inotropic effects at lower doses (3–5 μg/kg/min) for those patients with hypotension, and we administer it to patients to improve MAP in the perioperative period when volume expansion is not adequate or other disease states prevent larger volume expansion. We will consider holding the infusion of an immunosuppression induction agent or administering sodium bicarbonate or calcium carbonate during intraoperative hypotensive episodes.

Emergence and Postoperative Considerations

Patients who receive an intraoperative muscle relaxant should receive a neuromuscular blockade reversal agent such as neostigmine prior to extubation. Failure to reverse neuromuscular blocking agents is associated with increased risk of postoperative pulmonary complications [56]. Standard practice at our center is to extubate patients in the operating room at the conclusion of the operation. Kidney transplant patients rarely require postoperative

Table 1 Intraoperative kidney transplant recipient phases

	Considerations
Premedications	• Beta-blockade • Glucose monitoring with insulin therapy • H_2 blocker or PPI • Antibiotic prophylaxis • DVT prophylaxis • Metoclopramide for gastroparesis • Acetaminophen and ondansetron for PONV
Intraoperative monitoring	• Pulse oximetry with capnography • ECG leads • Noninvasive blood pressure monitoring • Peripheral venous access (14- or 16-gauge IV) • Peripheral nerve monitoring • Consider invasive CVP and/or blood pressure monitoring or TEE if indicated
Anesthetic agents	• GA or EA, can consider TIVA • Propofol, fentanyl, lidocaine • Cisatracurium, rocuronium, succinylcholine (if K+ <5.0) • Isoflurane for maintenance
Fluid management	• Slightly hypervolemic, 2.5–3.5 L • CVP 8–15 • Balanced crystalloid solution • Mannitol, furosemide at unclamp • Albumin may be given, prbcs if indicated
Hemodynamic management	• MAPs 70–90 mmHg • Minimize vasopressor support • Dopamine for inotropic support not for renal blood flow perfusion
Emergence	• Neostigmine • Extubation

critical care, although nursing assessments including hourly urine output measurements in the first 24 h are often requested. Postoperative pain control for kidney transplant recipients is usually through oral narcotics and intermittent IV pain medications such as hydromorphone. Hydromorphone is preferred to morphine, which has toxic metabolites that accumulate with renal impairment [57]. We also schedule acetaminophen and consider renally dosed gabapentin for neuropathic, incisional pain. Transversus abdominis plane (TAP) blocks for acute postoperative pain relief in kidney transplant recipients have been met with varied responses. One study showed decreased opioid consumption intraoperatively and in the first 24 h postoperatively [58], while another did not reduce 24-h morphine requirements [59]. We have utilized TAP blocks in selected patients with severe postoperative pain, and it has improved pain control when used as a rescue method in the recovery room at our institution.

Conclusions

Intraoperative considerations for the renal transplant recipient are essential as adequate restoration of blood flow to the renal allograft with adequate perfusion pressures to allow for immediate diuresis and function influences short- and long-term outcomes on graft and patient survival [6, 9, 35–37]. While optimal fluid loading conditions are unclear at this time, adequate hydration (CVP 8–15 cmH_2O) with a balanced crystalloid (60–90 mL/kg) to maintain an acceptable MAP for perfusion (70–90 mmHg) without the use of a vasopressor is key. The utilization of albumin and diuretics as well as the minimization of cardiodepressants and peripheral vasodilators such as inhaled anesthetics, propofol, and narcotics should be considered (Table 1).

Compliance with Ethical Standards

Conflict of Interest Rachel Forbes, Adam King, and Beatrice Concepcion declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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