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Anesthesia for Kidney Transplantation-A Review

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Abstract

Kidney transplant anesthesia can be a mentally challenging yet rewarding aspect of the anesthesiologist's job. End stage renal disease (ESRD) patients tend to have a medical history that leads to very complex physiology. In this article we will review the pathophysiology of ESRD, the effects of ESRD on other body systems, and how it effects the perioperative management of the ESRD patient.

Keywords: Pulmonary congestion; Kidney transplantation; Co-morbidity; Cardiomyopathy; Echocardiography

Introduction

Kidney transplantation is a process of attaching new kidneys to replace previously diseased kidneys. In most cases, the need for kidney transplantation results from end stage kidney disease resulting from glomerulonephritis, chronic interstitial nephritis or obstruction, and hereditary or cystic disease [1]. End stage renal disease (ESRD) is the last stage of chronic kidney disease (CKD) when kidneys are functioning at 10-15% of their normal capacity and renal replacement therapy becomes necessary. In the United States, the prevalence of ESRD is 1738 per million people. The number of people with ESRD is increasing and new cases are 3.5 times higher among African Americans than among whites. Treatment was limited to chronic hemodialysis and peritoneal dialysis until 1954 when Dr. Joseph Murray performed the first successful kidney transplant [2].

The mainstay of therapy remains chronic dialysis treatment however; a minority of patients is selected for kidney transplantation after exhaustive evaluation. Of these, most transplantation occurs in patients receiving donated kidneys from living related donors (23 per million people) compared to patients receiving deceased donor transplantation (2.5 per million people) [2]. Dialysis therapy has been found to be very expensive constituting up to 5% of the Medicare program expenditure in the US although dialysis patients comprise only 0.5% of the beneficiaries [3]. Another study in Greece concluded that dialysis treatment was more expensive than renal transplantation [4]. In addition, the 5 year survival rate in patients with transplanted kidneys is 70% compared to 30% in patients on hemodialysis [5]. Even recipients of marginal kidney transplants enjoy higher survival and quality of life compared to patients who stayed on dialysis [6]. Marginal transplants are considered to be grafts from older donors, donors with long-standing hypertension or diabetes mellitus, non-heart-beating cadaver donors and grafts with prolonged cold preservation time.

As increasing number of patients are being considered and are becoming eligible for transplantation and the median wait time has increased to 2.3 years [7]. During this period, patients are thoroughly evaluated and medically optimized. Medical optimization is one of the requirements to remain on the transplantation list [8,9]. Patients scheduled to undergo kidney transplantation are often among the most complex patients that an anesthesiologist may encounter. The goal of perioperative evaluation is to establish- a perioperative management plan given that patients presenting for transplantation are often chronically ill with conditions such as diabetes mellitus, hypertension, coronary artery disease and their complications. Most patients would have been initiated on either hemodialysis or peritoneal dialysis and present to the anesthesiologist with a long list of medications. The goal of this article is to review the perioperative management of patients undergoing kidney transplantation.

Pre-operative Considerations

With advances in surgical and anesthetic techniques, older and more medically complex patients are being considered for renal transplantation. Most patients presenting to anesthesiologists for pre-surgical evaluation for transplantation would have had thorough medical evaluation and follow-up to optimize their comorbidities as part of routine preparation for transplantation [2,6]. Absolute contraindications to transplantation include active infection, untreated malignancy, and predicted patient survival less than 5 years, risk of transplant graft loss greater than 50% at 1 year, inability to comply with immunosuppression regimen, and immunosuppression predicted to cause a life threatening complication [8,10]. After a donor kidney becomes available, it is matched to a recipient as best as possible by blood cross matching, HLA typing, and testing donor T-cell against recipient serum [11].

Cardiovascular

The risk of cardiovascular disease is 10 to30 times higher in dialysis patients than in the normal population and over 50% of deaths in dialysis patients result from cardiovascular disease [2,12]. As a result, a careful evaluation of the cardiovascular system is required in patients being considered for transplantation. Special emphasis should be paid to the assessment of intravascular volume status, presence of hypertension, and anemia [6]. A baseline 12 lead ECG should be obtained and resting transthoracic echocardiogram should be used to assess heart function for evidence of dilated cardiomyopathy and concentric hypertrophy which develop in response to chronically

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increased intravascular volume and increased after load usually present in these patients [10]. Guidelines published in July 2012 by ACC/AHA: "Cardiac Disease Evaluation and Management among Kidney and Liver Transplantation Candidates" facilitate the efficient cardiac evaluation in these patients [13]. The guidelines focus on obtaining a thorough history, accompanied by physical examination to identify any active cardiac condition such as unstable coronary syndrome, severe valvular disease, decompensated heart failure, and significant arrhythmias. This structural evaluation is followed by assessment of functional status.

In general, "functional status" is an indication how well patients are coping with their day-to-day activities despite ESRD and may reveal evidence of cardiovascular disease given that patients with ESRD are less likely to experience chest pain during myocardial ischemia or infarction [14]. Noninvasive stress testing should be considered in patients without active cardiac disease but who have 3 or more risk factors associated with coronary artery diseases (CAD) as published in the guidelines. These risk factors include diabetes mellitus, prior cardiovascular disease, and duration of dialysis greater than 1 year, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension, or dyslipidemia. The risk factors were deemed relevant to transplantation candidates and were adapted at the 2007 Lisbon Conference [15]. The type of noninvasive testing used for further risk stratification (dobutamine stress echocardiography versus myocardial perfusion scintigraphy), is at the discretion of the perioperative evaluator.

Patients waiting on the transplant list beyond one year, should be screened annually with 12 lead ECG and possibly resting TTE, although the usefulness of periodic screening for resting LV function while on the transplantation list is uncertain except in patients with moderate aortic stenosis who should be treated as rapid-progressors and therefore have yearly resting echocardiography [13]. Recent studies have suggested that elevated pulmonary artery pressures are associated with adverse outcomes after renal transplantation [16]. Renal transplant candidates found to have pulmonary hypertension on TTE should have right heart catheterization to confirm the diagnosis and full evaluation performed by a physician with expertise in pulmonary hypertension management [13]. In summary, the goal of cardiovascular evaluation is to diagnose active or chronic CAD, determine the patient's functional status and optimize therapy prior to renal transplantation.

Pulmonary

The respiratory challenges facing the anesthesiologist during kidney transplantation surgery arise mostly from volume overload and pulmonary congestion. This usually results in hypoxemia and occasionally hypercapnia. In patients undergoing peritoneal dialysis, diaphragmatic splinting may lead to basal lung atelectasis and result in arterio-venous shunting [17]. Dialysis and fluid removal prior to surgery is helpful with alleviating pulmonary congestion. There are no specific indications for further pulmonary work-up in kidney transplant patients unless the patient has other co morbid lung diseases.

Gastrointestinal

Uremia from kidney failure may lead to gastro paresis. Additionally, many ESRD patients suffer from diabetes mellitus and autonomic neuropathy and should therefore be treated with full stomach precautions. Preoperative treatment with a Histamine2 blocker and metoclopramide are recommended [18]. Hepatitis C virus (HCV) infection is associated with membranous nephropathy and membrano proliferative glomerulonephritis and is common among dialysis patients. In addition, patients on chronic hemodialysis are at an increased risk of acquiring HCV infection as a result of frequent blood transfusions. HCV infection is a risk factor for death in renal transplantation patients who develop sepsis and septic shock [19].

Renal and metabolic

Since patients with ESRD are either on peritoneal dialysis or hemodialysis, they may present with electrolyte and metabolic abnormalities such as hyponatremia, hyperchloremia, hyperkalemia, hypocalcemia, hypermagnesemia and metabolic acidosis. The severity of these electrolyte derangements is usually related to the timing of the patient's last dialysis session. Perioperative hyperkalemia is most concerning in the perioperative period. Since these patients are usually chronically hyperkalemic, the ECG changes usually seen in hyperkalemia such as peaked T-waves, flat P waves, increased PR interval or widening QRS may not be present until much higher values are reached. Consequently, It is important to have periodic checks to detect hyperkalemia. To avoid complications of hyperkalemia, treatment with insulin, sodium bicarbonate, and beta-agonist should be considered if the potassium is greater than 5.5 mEq/L. Routine preoperative electrolyte evaluation should be obtained prior to surgery [17,18].

Hematologic

Patient with ESRD usually presents with normochromic, normocytic anemia. Anemia has been linked to cardiovascular morbidity and mortality and Harnett et al. found the independent relative risk of mortality in dialysis patient to be 1.18 per 1.0 g/dl decrease in hemoglobin level [20]. Anemia in ESRD results from impaired erythropoiesis from decreased erythropoietin synthesis and release, and also decreased red blood cell life span. In addition, increased hemolysis, repeated blood loss during dialysis, uremia induced bone marrow suppression and iron, folate, vitamin B_6/B_{12} deficiencies all contribute to anemia [17].Most patients are treated with synthetic erythropoietin to increase hemoglobin. The anemia is well tolerated in most patients due to compensatory increases in cardiac output, 2, 3-DPG and a right ward shift of oxygen dissociation curve which results in improved tissue oxygenation [21].

The correction of decreased erythropoiesis, with erythropoietin, aids oxygen transport and decreases cardiac output, heart rate and cardiac workload, which leads to a decrease in left ventricular hypertrophy and overall improvement in cardiac status [22]. Exercise capacity, cognitive and brain function and quality of life also improve. Ultimately, mortality is reduced [23,24]. Patients may also be thrombocytopenic from uremia associated thrombocytopathia. A thorough history should be obtained to detect possible platelet dysfunction. Preoperative prothrombin time (PT), Partial thromboplastin time (PTT), INR, complete blood count (CBC), and liver function tests should be obtained during the pre-transplantation work-up [18].

Endocrine

Diabetes mellitus is the most common co-morbidity in patients with ESRD. Patients with diabetic nephropathy are known to have higher mortality rates than other patients with other causes of ESRD [25].The risk of cardiovascular disease is high, hence the need to screen for and treat coronary artery disease in diabetic patients undergoing transplantation. Good glycemic control is important before and during transplant and is associated with a lower mortality [26]. Preoperatively, immediate point of care glucose should be checked prior to surgery. Glucose control between 120-200 mg/dL is recommended rather

that tight glycemic control [18]. Hyperphosphatemia resulting from decreased excretion of phosphate and hypocalcemia due to reduced absorption of calcium from the GI tract and vitamin D deficiency are very common. This leads to a secondary hyperparathyroidism and demineralization of bone possibly leading to pathologic fractures [27].

Nervous system

CNS manifestation such as malaise, fatigue, inability to concentrate, seizures and coma can be seen in patients who are uremic. These complications are reduced with dialysis [17]. Other manifestations such as prior stroke may be seen due to the vascular disease that often accompanies ESRD. Peripheral and autonomic neuropathies can lead to orthostatic hypotension and silent myocardial ischemia [18].

Intra-operative Considerations

Pharmacology

ESRD not only affects the pharmacokinetics and pharmacodynamics of drugs excreted by the kidneys, but also modifies the disposition of other drugs through changes in protein binding or hepatic metabolism [5]. Hepatic drug metabolism is influenced either through induction or inhibition of hepatic enzymes or by alteration of hepatic blood flow, and the production and elimination of metabolites. Changes in body fluid distribution and circulatory volume which occur in patients with ESRD also affect drug disposition [28]. Anesthesiologists should therefore be knowledgeable about the changes in the metabolism of each drug administered in the perioperative period. The distribution and clearance of the short acting benzodiazepine midazolam remains relatively unchanged making it a drug of choice for anxiolysis in this group of patients [29].

Induction agents

The pharmacokinetics and pharmacodynamics of the hypnotic Propofol are unchanged in ESRD patients [30]. Propofol is mainly metabolized in the liver and its metabolites do not have pharmacological activity. Furthermore, it has been shown to be safe for the induction and maintenance of anesthesia in patients with renal failure. Infusion dose requirements have also been found to be similar in ESRD patients and patients with normal renal function although shorter emergence times have been noted in ESRD patients when compared with patients with normal renal function. Thiopental is another inducing agent that is almost entirely metabolized in the liver. Its breakdown products are excreted by the kidneys and the gastrointestinal tract. Traces are excreted unchanged in the urine. No permanent effects of this agent on kidney function have been recorded.

Neuromuscular blocking agents

Succinylcholine is frequently used in general anesthesia to facilitate tracheal intubation because of its rapid onset and brief duration of action. It may however increase serum potassium concentration, which can result in cardiac arrhythmias and even cardiac arrest; especially in patients with ESRD. Therefore, succinylcholine should be used with caution in patients with ESRD. Long-acting non-depolarizing neuromuscular blocking agents are largely eliminated by renal excretion and the effects of long-acting non-depolarizing neuromuscular blocking agents may be significantly prolonged in patients with ESRD, leading to a high rate of residual blockade at the end of surgery. Therefore, in patients with ESRD, muscle relaxants that are not primarily dependent on renal function should be used for general anesthesia. Cisatracurium is intermediate acting muscle relaxant. It is metabolized through Hofmann elimination and produces a metabolite, Laudanosine, which is partially eliminated through the kidneys hence, has a slightly prolonged elimination half-life in patients with renal failure. Overall, the duration of action of cisatracurium is slightly prolonged in renal disease [9].

Other muscle relaxants such as vecuronium and rocuronium are also eliminated relatively independent of kidney function. Both drugs are mainly metabolized by the liver, but have metabolites that are excreted by the kidney and liver. The duration of action of vecuronium and rocuronium in patients with renal failure has been reported to be slightly prolonged and a cumulative effect has been noted with repetitive administration. Cis atracurium is the preferred muscle relaxant in patients with ESRD [31,32].

Opioids

Perioperative analgesics should be administered with care in ESRD patients undergoing transplantation given that these agents or their active metabolites depend on renal excretion and may accumulate [10]. The effect of morphine is prolonged in patients with chronic renal failure as a result of the accumulation of its active metabolite morphine-6-glucuronide [33]. Similarly, the administration of high or repeated doses of meperidine in these patients may lead to seizures due to the accumulation of its metabolite, normeperidine [34]. The elimination of oxycodone is also impaired in ESRD patients undergoing renal transplant [10]. Importantly, the pharmacokinetics of fentanyl, alfentanil, sufentanil are not altered in chronic renal failure, because the metabolites are inactive and are unlikely to contribute to the opioid effect even if they do accumulate [35]. Remifentanil, a very short acting opioid is metabolized in the peripheral tissues by an esterase enzyme and requires no change in dosing compared to patients with normal renal function. However, total drug clearance and the volume of distribution may be significantly increased [36].

Inhalational agents

All potent inhalational agents cause a decrease in the renal blood flow and glomerular filtration rate in proportion to the dose. Many also release fluoride as a byproduct and fluoride has been linked to high output renal failure. Although fluoride is a major metabolite of isoflurane, the extent of its metabolism is very small such that the amount of fluoride produced is unlikely to cause renal damage. It can be used in anesthesia for renal transplantation. Another inhaled agent, Sevoflurane, is metabolized to compound A by carbon dioxide absorbents used in standard anesthesia machines. When sevoflurane is used with lower fresh gas flows, compound A can accumulate within the anesthesia machine gas circuit [37]. Compound A has been shown to be nephrotoxic in rats but has not been reported to increase renal dysfunction in humans with pre-existing renal disease [38,39]. In fact, Conzen et al. reported that low-flow sevoflurane anesthesia was safe and did not alter kidney function in patients with pre-existing renal disease [40]. Hence, low-flow sevoflurane anesthesia can be safely used in renal transplant recipients. Similarly, desflurane can also be used in patients with renal dysfunction and no deterioration in renal function has been found in patients with pre-existing renal disease who were administered desflurane [41].

Anesthetic Management

Kidney transplantation is usually performed under general endotracheal anesthesia although they can be done under spinal anesthesia in rare cases. In fact, early kidney transplants were done under spinal anesthesia and some centers in the US still perform

neuraxial anesthesia for kidney transplantation. General endotracheal anesthesia provides stable hemodynamics, excellent muscle relaxation, and predictable depth of anesthesia [10]. Combined techniques using GETA and epidural analgesia can also be employed. Hemodynamics and renal function have not been reported to differ significantly between techniques [42]. Adequate monitoring is essential in patients undergoing kidney transplantation. Standard ASA monitors may be sufficient if the patient has no other co morbidities except ESRD. Most patients, however, will benefit from CVP monitoring and possibly invasive arterial blood pressure monitoring given the expected large swings in hemodynamic parameters during surgery. Patients with severe coronary artery disease, left ventricular dysfunction, valvular abnormalities, or pulmonary hypertension may also benefit from advanced intraoperative monitoring such as pulmonary capillary wedge pressure monitoring or intraoperative transesophageal echocardiography [5]. Aggressive volume expansion to a target CVP of 10-15mmHg is optimal. This volume expansion is associated with increased renal blood flow and improved graft function [5].

CVP invariably declines in the late intraoperative and immediate postoperative period despite positive fluid balance and vigorous fluid resuscitation. The etiology is unclear but may be due to increased vascular permeability and alterations in vascular tone accompanying surgery. Fluid redistribution in different compartments as a result of preexisting vascular permeability may also be responsible for the decrease in CVP. Graft acute tubular necrosis has been reported to be lower in patients who are vigorously hydrated [43-45]. Ferris et al. found no correlation between the decrease in CVP and fluid balance although the fluid balance of recipients correlated strongly with immediate post-operative graft function [46]. The maximum decrease in CVP values occurred between the operating room and intensive care unit [46].

Other agents used to promote renal blood flow such as dopamine, dobutamine and fenoldopam) as well as osmotic and loop diuretics (mannitol and furosemide) have been proposed as aiding kidney function after reperfusion. Of these, only mannitol has been shown to decrease the incidence of acute tubular necrosis [5]. Two meta-analyses have shown a negative effect of dopamine on renal function in acute renal failure [47,48]. In contrast, dobutamine can be used as a positive inotrope for patients with a low cardiac output [2]. Normotension or slight hypertension should be maintained to help graft function, but one should be weary of using alpha agonist, as the vasoconstriction may interfere with renal perfusion [5]. The overall anesthetic goal for the newly transplanted kidney is to maintain intravascular volume and avoid decreased perfusion to the new kidney. Normal saline is the intra-operative intravenous fluid of choice in renal transplant recipients. Potassium-containing fluids, such as lactated Ringer's solution, are avoided in order to minimize the risk of development of hyperkalemia. Metabolic acidosis may develop following the administration of large volumes of normal saline. The observed acidosis likely due to the chloride infused. The resulting hyperchloremic metabolic acidosis can further lead to extracellular potassium shift, and hyperkalemia. Nevertheless, normal saline is still the fluid of choice in patients undergoing transplantation [2].

Colloids may be considered in recipients with severe intravascular volume deficits who require high-volume resuscitation [49]. Albumin, a normal endogenous colloid with a wide safety margin is recommended with large fluid deficit. Synthetic colloids that have widely replaced albumin in clinical practice; dextrans, gelatins and solutions of hetastarch; do not seem to be preferable to albumin [49]. Colloids have been reported to adversely affect renal function and may increase bleeding complications [50]. The high potassium and calcium content of gelatins renders them inapplicable for perioperative care during renal transplantation [51]. Dextran solutions have been associated with severe hypersensitivity reactions and coagulation problems [52,53]. Hydroxyethyl starch (HES), although a synthetic colloid is an alternative to Albumin. HES are a medium molecular weight solution and have the lowest in vivo molecular weight above the threshold for renal elimination. It is also easily degradable. A study concluded that HES given at a maximum dosage of 15 ml/kg/day to the donor had no detrimental effect on renal function in the graft recipient. Sufficient amounts of crystalloids should, however, be infused along with HES [54].

Postoperative Care

Most newly transplanted patients can have their neuromuscular blockade reversed and their trachea extubated at the end of surgery. Many patients do not require intensive care unit admission. In fact, most patients are cared for in the medical-surgical floor. Regardless of postoperative ward destination, intravascular volume status and urine output should be monitored closely. These patients need close monitoring in a specialized ward. Sudden decrease in urine output may warrant surgical re-exploration [11]. Transplanted patients requiring prolonged mechanical ventilation postoperatively, have a worse outcome compared with patients who were extubated at the end of surgery [55]. Post-operative pain relief is essential after renal transplantation, as inadequately controlled pain can lead to agitation, tachycardia, hypertension and an increased risk of pulmonary complications. Postoperative pain can either be managed with epidural analgesia if available or by patient-controlled analgesia. Morphine, fentanyl or hydromorphone delivered by patient-controlled analgesia can provide sufficient pain relief. Epidural analgesia provides superior analgesia but may occasionally result in hypotension and decreased renal perfusion further complicating graft survival [11]. Patient controlled analgesia while less effective for pain control is less likely to cause hypotension. The use of non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided [56]. The use of high-dose NSAIDs in patients with chronic kidney disease has been shown to increase the risk of rapid progression of the disease in the elderly age group. Cyclo-oxygenase-2 enzyme inhibitors have also been reported to be nephrotoxic in transplant recipients and in patients with impaired renal function [57].

Immunosuppressive Therapy

Immunosuppression varies by center and is usually protocol based. Regimens can be high dose conventional regimen or an antibody induction regimen. The conventional regimen consists of a calcineurin inhibitor (cyclosporine or tacrolimus), a corticosteroid, and an antimetabolite (mycophenalte mofetil or azthoprine). The antibody induction regimen, which has shown better graft outcomes, uses lower doses of the conventional medications with the addition of an antibody directed at T-cells antigens: anti-lymphocyte antibodies (i.e. Thymoglobulin, alemtumzumab, OKT3) or interleukin-2 receptors antagonist: Basiliximab (trade name Simulect) or Daclizumab (trade name Zenapax) [58]. The antibody induction regimen has been shown to result in better graft outcomes. Induction of immunosuppression usually begins with the corticosteroid and an antilymphocyte administered shortly before reperfusion of the renal graft [18].

Summary

ESRD patients and kidney transplantation present significant challenges, for the anesthesiologist, in the perioperative period. The optimal approach to anesthetic delivery is to develop an anesthetic plan tailored to the patient's specific co morbidities. Overall optimization of the patients other co morbidities in the preoperative period, close intraoperative monitoring and optimization of fluid status and hemodynamics as well as appropriate use of anesthetic agents are key to kidney transplantation success.

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