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Anaesthesia for renal transplant surgery

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Renal transplantation is the preferred therapeutic option for patients with end-stage renal disease. Survival rates are much higher in patients who receive a transplant. Patients with renal failure have significant concomitant medical conditions, such as cardiovascular disease. This article provides an overview of the important issues to be considered in patients undergoing renal transplant, and discusses the anaesthetic management of these patients.

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In recent years, tremendous strides have been made in the general care of patients with end-stage renal disease (ESRD). By definition, ESRD begins when renal replacement therapy is initiated. Once the kidneys fail, the patient has three management options: haemodialysis (HD), peritoneal dialysis (PD) or transplantation. Over the past decade, improvements in immunosuppressive medication, organ procurement, patient preparation and surgical techniques have resulted in a significant increase in survival rates after renal transplantation (1, 2). Furthermore, renal transplantation has been shown to confer a greater survival benefit than maintenance dialysis. The estimated number of additional life-years gained from renal transplantation have been found to vary from 8 years in a 60-year-old diabetic recipient to 31 years in a non-diabetic recipient aged between 20 and 44 years (3, 4). Moreover, in dialysis patients, the left ventricular function tends to deteriorate with time (5). Valvular disease, in particular aortic stenosis, has also been shown to progress markedly over the years in dialysis patients (6). Therefore, earlier transplantation is advantageous to ESRD patients on dialysis.

The kidney donor pool has been expanded to include those who might have been deemed unsuitable in earlier times. The presence of certain pre-transplant correlates of diminished graft survival, such as advanced donor age, long-standing donor hypertension or diabetes mellitus, non-heart-beating cadaver donor and prolonged cold preservation time, has been used to characterize an organ as being of marginal quality (7–9). Ojo et al. (10) found that, on average, recipients of marginal kidney transplants lived 5 years longer than transplant candidates who remained on dialysis, whereas ideal cadaveric transplant recipients had a 13-year survival benefit. Rabbat et al. (11) have also shown a long-term survival advantage associated with cadaveric renal transplantation over dialysis. This difference was found to be more striking in patients in whom end-stage renal failure was caused by diabetes and glomerulonephritis.

Dialysis is considered to be one of the costliest treatment modalities in medicine. In a study by Joyce et al. (12), the annual per-patient cost was found to increase by 150% in diabetics and 140% in those without diabetes following the onset of ESRD. In the same study, it was shown that 5% of Medicare programme expenditure in the USA was for ESRD patients, although they constituted only 0.5% of the beneficiaries. In another study in Greece, the average cost of a single dialysis session was estimated to be 240 euros, and the aggregate economic impact was calculated to exceed 250 million euros per annum (13). Furthermore, in this study, it was reported that dialysis was more expensive than renal transplant, the cost of which was calculated to be 22,500 euros according to the estimate of the Hellenic National Transplant Organization in 2003. Thus, it is more economically feasible to perform a renal transplant in patients with ESRD.

The aims of this review are to provide an overview of the pre-operative considerations involved in

patients undergoing renal transplant, and to discuss the anaesthetic management of these patients.

Pre-operative assessment

Patients with end-stage renal failure suffer from various concomitant medical diseases. Their medical history is complex and many systems are likely to be affected. Diabetes is the most common cause of ESRD, followed by hypertension (Fig. 1). Hence, it is important to take a full pre-operative history and also to evaluate the medications taken by the patients. The important medical and other issues to be considered in patients with ESRD, prior to transplant, are summarized in Table 1 and explained in detail below.

Table 1

Important pre-operative considerations prior to renal transplant.

Cardiovascular disease
Ischaemic heart disease
Congestive cardiac failure
Hypertension
Diabetes mellitus
Anaemia
Hyperparathyroidism and elevated calcium and phosphate
Dyslipidaemias
Infections
Hepatitis B
Hepatitis C
Newer cardiovascular risk factors
C-reactive protein
Homocysteine
Duration of end-stage renal disease
Centre effect

Cardiovascular disease

Cardiovascular disease is the major cause of increased morbidity and mortality in dialysis patients, and accounts for over 50% of deaths (14). The risk of cardiovascular disease is 10–30 times higher in dialysis patients than in the normal population. Following renal transplantation, the risk is decreased to twice that in normal subjects (15, 16). Several factors contribute to the development and progression of cardiovascular disease in patients on renal replacement therapy. These include both the traditional cardiovascular risk factors recognized in the general population and additional risk factors particular to chronic renal failure, such as volume overload with consequent hypertension (17, 18), anaemia (19) and disturbance of calcium phosphate metabolism (20).

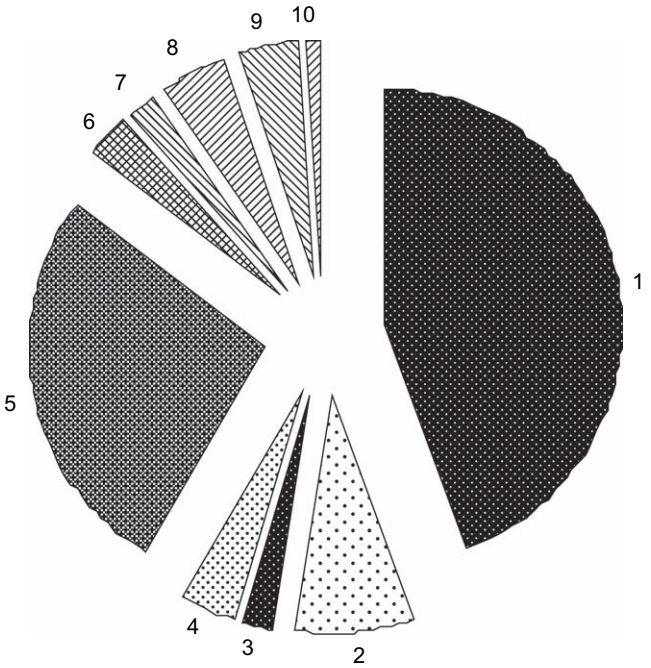

Fig. 1. Incidence of end-stage renal disease (ESRD) by primary diagnosis [data from US Renal Data System (USRDS) 2006 Annual Data Report: Atlas of End-Stage Renal Disease in United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes, Digestive and Kidney Diseases, 2006]. 1, Diabetes mellitus (44.9%); 2, glomerulonephritis (8.2%); 3, secondary glomerulonephritis/vasculitis (2.1%); 4, interstitial nephritis/pyelonephritis (4.1%); 5, hypertension/large vessel disease (26.6%); 6, cystic/congenital/hereditary disease (3.4%); 7, neoplasms/tumours (2.1%); 8, miscellaneous (4.6%); 9, aetiology uncertain (4.1%); 10, missing (1.1%).

All patients should be investigated for cardiovascular disease when they are accepted onto the transplant waiting list. Various angiographic studies have demonstrated a high prevalence of clinically silent ischaemic heart disease in these patients, especially in those with concomitant diabetes mellitus (21–23). As the resting electrocardiogram (ECG) is often abnormal in these patients, standard treadmill tests are difficult to interpret (24). Hence, dobutamine stress echocardiography or thallium dipyridamole stress tests should be considered (23, 25). Coronary angiography should be carried out in patients showing reversible ischaemia.

Congestive cardiac failure is also more prevalent in dialysis patients. When ESRD patients with congestive heart failure as a result of reduced left ventricular ejection fraction (LVEF) present for kidney transplantation evaluation, they are generally considered to be at high risk for surgery. However, Wali et al. (26) demonstrated that kidney transplantation could be performed safely in ESRD patients with decreased LVEF, advanced heart failure and without inducible ischaemia. In their study, renal transplantation

resulted in an increase in LVEF in more than 86% of patients, and was associated with an improvement in New York Heart Association (NYHA) functional status in more than two-thirds of patients. Furthermore, they reported that the duration of dialysis therapy before kidney transplantation was the only significant factor that predicted the normalization of LVEF. However, subjects in this study were relatively young.

Hence, all dialysis patients with reduced LVEF must be initially evaluated for underlying ischaemia, and their medications for heart failure [β-blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker] should be optimized. These patients can then be assessed for kidney transplantation, especially those in the younger age groups.

Hypertension

Hypertension is a common clinical problem in renal transplant recipients, and plays an important role in causing cardiac damage by producing left ventricular hypertrophy, which predisposes the patient to ischaemia (27). The impairment of coronary perfusion in a hypertrophic heart results in regional impairment of left ventricular contraction and left ventricular dilatation, leading to systolic dysfunction (28). The risk of cardiovascular death in patients on dialysis has been reported to be 2.2 times greater in those with a pre-dialysis blood pressure of 130/80 mmHg or greater than in those with a blood pressure of less than 130/80 mmHg (18). Foley et al. (17) have reported that, after adjusting for age, diabetes, ischaemic heart disease, haemoglobin and serum albumin, each 10-mmHg rise in mean arterial blood pressure is associated with concentric left ventricular hypertrophy and the development of ischaemic heart disease and cardiac failure. An inverse relationship has been shown to exist between the severity of hypertension and graft survival (29).

A blood pressure of 140/90 mmHg has been shown to minimize the occurrence of left ventricular hypertrophy and death in dialysis patients (17). Hence, a value of 140/90 mmHg or less should be set as the target blood pressure (30). Ambulatory blood pressure monitoring is not strictly necessary for routine monitoring in HD patients.

For the control of high blood pressure, ACE inhibitors should be used, as these agents have been found to confer a better prognosis in patients with a high risk of cardiovascular events (31). Angiotensin-II receptor antagonists should be used when an ACE inhibitor-induced cough is present, and also in heart failure. Calcium antagonists can be given in the elderly, but short-release preparations should be avoided.

Diabetes

Diabetic nephropathy is the most common cause of ESRD in Europe, Japan and the USA. Patients with diabetic nephropathy and ESRD are known to have higher mortality rates than those with other causes of ESRD. Diabetic patients with renal failure have an increased risk of cardiovascular disease. Hence, screening and treatment of coronary artery disease are essential in diabetic patients undergoing transplantation. Good glycaemic control is also important before and during transplant, and is associated with a lower mortality.

Norio et al. (32) studied the peri-operative ECGs and invasive haemodynamic and oxygenation parameters in patients undergoing renal transplantation. They reported an increased incidence of QT dispersion in the pre-operative ECG and a higher pre-operative heart rate and mean arterial pressure in diabetics than in non-diabetics. Following pre-anaesthetic volume loading, hyperdynamic circulation was noted in all patients, which subsided during anaesthesia. Although intra-operative cardiac dysrhythmias were not noted in any of the diabetics in this study, it is suggested that ECG monitoring should be performed intra-operatively in all diabetics for arrhythmias.

Diabetic patients undergoing renal transplant are susceptible to accelerated peripheral vascular disease (33). Diabetic foot disease can be troublesome post-transplant. Post-transplant diabetes mellitus is also known to develop as a complication of immunosuppression, specifically steroids and calcineurin inhibitors.

Anaemia

Anaemia is a known complication of ESRD and is also linked to cardiovascular morbidity and mortality. In chronic renal failure, decreased left ventricular capillary supply increases the critical oxygen diffusion distance in the myocardium (which is hypertrophic in renal failure), predisposing it to ischaemia and, consequently, failure. In a study by Harnett et al. (19), the independent relative risk of mortality in dialysis patients was calculated to be 1.18 per 1.0-g/dl decrease in haemoglobin level. Mix et al. (34) reported that the prevalence of anaemia (haematocrit $<36\%$) was 76% at transplantation and fell to 21% 1 year post-transplant.

The correction of anaemia with erythropoietin increases oxygen transport and decreases cardiac output, pulse rate and cardiac workload, which leads to a decrease in left ventricular hypertrophy, thereby improving cardiac status (35). Furthermore, it also improves exercise capacity, cognitive and brain function and quality of life, and also reduces mortality (36, 37). However, erythropoietin therapy has been found to increase blood pressure in up to 30% of dialysis patients (38). The correction of anaemia has also been found to improve uraemic coagulopathy, increase blood viscosity and decrease erythrocyte deformability, thus predisposing to thrombus formation (39). Hence, a gradual correction of anaemia with a target haemoglobin level of around 12 g/dl should be considered for all patients.

Parathyroid hormone, calcium and phosphate

Elevated serum calcium and phosphate, secondary hyperparathyroidism and the administration of phosphate-chelating agents may play a role in the pathogenesis of cardiovascular disease in chronic renal failure. A high degree of fibrosis and myocardial calcium content can lead to the development of myocardial hypertrophy and diastolic dysfunction of the left ventricle (40). Secondary hyperparathyroidism and increased calcium $\times$ phosphate product have been found to be associated with calcification of the cardiac valves and coronary arteries (41, 42). It has been suggested that hyperphosphataemia is mainly responsible for cardiac valve calcification, and hence should be efficiently controlled (43). Calcium-based chelators are widely used for phosphate control; however, high doses are required, which can lead to frequent episodes of hypercalcaemia, thus contributing further to metastatic calcification.

Dyslipidaemia

The prevalence of dyslipidaemia in chronic renal failure is higher than that in the general population. Higher levels of serum lipoprotein-A seen in chronic renal failure have been found to contribute to atherosclerosis, leading to an increased incidence of cardiac events (44). Hence, serum lipid levels should be decreased using a strategy combining dietary modifications and lipid-lowering agents.

Other cardiovascular risk factors

In the last decade, evidence has been increasing that atherosclerosis is an inflammatory disorder (45). C-reactive protein (CRP), a marker of micro-inflammatory state, is a potent predictor of cardiovascular mortality in both the general and ESRD population. CRP has been found to be chronically elevated in one-third to two-thirds of dialysis patients (46, 47). Oh et al. (48) have demonstrated that CRP strongly correlates with coronary calcifications in young ESRD patients, not only undergoing dialysis but also after renal transplantation. In chronic renal failure patients, CRP levels have been found to be associated with malnutrition and increased cardiovascular risk and mortality (49). Furthermore, increased levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1), tumour necrosis factor-α, IL-6 and IL-13, have also been found to be associated with higher rates of mortality in HD patients (50).

Homocysteine is another cardiovascular risk factor that is elevated in chronic renal failure and remains so even after kidney transplantation. Homocysteine has been found to predict cardiovascular mortality in ESRD patients and morbidity after transplantation (51, 52). Oh et al. (48) have reported that hyperhomocysteinaemia contributes significantly to coronary artery calcification, independent of CRP, parathyroid hormone and calcium phosphate load.

Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of nitric oxide (NO) synthase. It has been hypothesized that ADMA accumulation in renal failure inhibits NO-induced vasodilatation, and thus could contribute to hypertension and cardiovascular disease (53).

Hepatitis C

Hepatitis C virus (HCV) infection is linked to chronic renal disease. Chronic infection with HCV is associated with membranous nephropathy and membranoproliferative glomerulonephritis with or without cryoglobulinaemia (54). Patients on chronic HD are at an increased risk of acquiring HCV infection as a result of frequent blood transfusions and HCV-contaminated dialysis equipment. Various studies have reported that the relative risk for death in anti-HCV-antibody-positive patients is significantly higher than that in anti-HCV-antibody-negative patients after adjusting for age, transplantation, duration of dialysis and race (55, 56). Hepatocellular carcinoma and liver cirrhosis are serious complications of HCV infection and could contribute to the high mortality in the HCV-positive group (57, 58). Sepsis has been shown to be another significant cause of death in HCV-positive patients with renal transplantation (59).

There is considerable debate about the effect of recipient HCV infection on renal allograft loss and

acute rejection in kidney transplantation. Numerous studies have reported a deleterious effect, with higher rates of acute rejection and allograft loss (60, 61). By contrast, an equal number of studies have reported outcomes that are comparable with those seen in recipients who are not infected with HCV (62, 63). The differences may possibly be the result of the influence of confounding factors, other than HCV infection, on renal allograft outcomes.

Human immunodeficiency virus (HIV) infection

The number of HIV-positive patients having ESRD has increased over the last couple of years. The various factors contributing to this increase are HIV-associated nephropathy, increased duration of survival of HIV-positive patients and increased survival of HIV-positive patients on dialysis.

The presence of HIV type 1 has traditionally been considered a contraindication for transplantation because of concerns that immunosuppression could increase viral load, and a stable patient could decompensate. However, the introduction of highly active antiretroviral therapy (HAART) has markedly improved the survival of HIV-infected patients because of excellent control of the viral load and fewer infections (64). Furthermore, because of the extremely low HIV viral load (<50 copies/ml), fresh T cells can be generated prior to transplantation (65).

Bhagani et al. (66) have compiled guidelines for renal transplantation in HIV-infected patients. A life expectancy of at least 5 years is considered to be appropriate before planning transplantation. Furthermore, the patients should have been on a stable HAART regimen for at least 6 months (CD4 count >200 cells/μl; HIV viral load <50 copies/ml). There should be no current acquired immunodeficiency syndrome (AIDS)-defining illness. Infections with resistant fungi and bacteria and untreated active chronic infections with cytomegalovirus (CMV) and *Mycobacterium* are considered as contraindications to transplantation. Advanced cardiopulmonary disease, a history of neoplasms, except adequately treated solid tumours with a disease-free period of more than 5 years, pregnancy and human T-cell lymphotropic virus type-1 positivity are also considered as contraindications to transplantation.

Before transplant, all patients should be vaccinated with pneumococcal, meningococcal and *Haemophilus influenzae* B vaccines. Patients should also be vaccinated with varicella, hepatitis A and B vaccines if they do not possess antibodies to these infections. Furthermore, routine pre-transplant assessment should include ophthalmological examination to rule out CMV retinitis, and cervical and anal smears for human papillomavirus-associated cervical and anal intraepithelial neoplasia.

Duration of ESRD and renal transplant outcome

Increased duration of pre-transplant ESRD is associated with poor graft and recipient outcome (67, 68). Goldfarb-Rumyantzev et al. (69) found that a longer duration of ESRD was associated with a worsening graft outcome; however, the association only became significant after 6 months of dialysis therapy, and, after 3 years, no significant change in risk was evident. In the same study, a longer duration of ESRD was reported to be associated with a worsening recipient survival when calculated from the time of transplant, becoming significant after 1 year of ESRD duration.

Kidney transplantation is associated with a significant improvement in azotaemia. By contrast, prolonged exposure to uraemic toxins has been demonstrated to affect myocardial contractility. Although the exact nature of such toxins has yet to be ascertained, various studies have demonstrated numerous potentially negative inotropic and chronotropic factors in the uraemic plasma (70, 71). Amann et al. (72) have reported that a prolonged exposure to these uraemic toxins can result in myocyte fibrosis and death. A longer duration of dialysis therapy results in a prolonged exposure of myocytes to these uraemic toxins, and hence may decrease the likelihood of improvement in LVEF in the post-transplant period. Similarly, Eknoyan et al. (73) have demonstrated that a longer duration of dialysis and decreased clearance of middle molecules (a component of the uraemic toxin) are associated with an increased risk of death from cardiac causes. Furthermore, increased atherogenesis during chronic renal failure and dialysis treatment may cause deterioration in the cardiovascular status of all potential transplant recipients, and of diabetic patients in particular (74).

The centre effect

Various studies have shown that centres performing lower numbers of transplants over a designated period of time show lower graft and patient survival rates. The centre effect in renal transplantation has been defined as the variation in centre-specific renal allograft outcomes beyond that which can be explained by random variation and adjustments for factors known to impact on these outcomes (75, 76).

Although some studies have shown that the centre effect is most significant only within the first year after transplantation (77), others have reported the persistence of the centre effect at 1 year post-transplantation and beyond (75, 76, 78). The centre effect has been reported to be lower in living donor transplants and negligible in human leucocyte antigen (HLA)-identical transplants. The degree of HLA matching has been reported to account for some of the variation seen between centres (79, 80). Physician and surgeon experience and careful and well-organized clinical management have been found to be important factors in determining a centre's success in renal transplantation (77, 81).

Anaesthetic management

Anaesthetic drugs

The most important risk factor for post-operative renal failure is poor pre-operative renal function (82). As subjects with ESRD have impaired renal function, it is important to avoid potentially nephrotoxic substances when anaesthetizing these high-risk patients (Table 2). Hepatic drug metabolism is also influenced by renal failure, either through induction or inhibition of hepatic enzymes or by alteration of protein binding and protein denaturation. Changes in body fluid distribution and circulatory volume also affect drug disposition. This causes changes in hepatic blood flow, which alter the production and elimination of metabolites (83, 84).

Table 2

Safety profile of drugs for anaesthesia.

Neuromuscular blockers		**Inhalational agents**	
Succinylcholine	+ (K <5.5 mEq/l)	Isoflurane	+
Atracurium	+	Sevoflurane	+
Cisatracurium	+	Desflurane	+
Mivacurium	+/–	Enflurane	–
Vecuronium	+/–	**Induction agents**	
Rocuronium	+/–	Propofol	+
Pancuronium	+/–	Pentothal	+
Intra-operative opioids		**Post-operative analgesics**	
Fentanyl	+	Morphine	+
Alfentanil	+	Fentanyl	+
Sufentanil	+	Paracetamol	–
Remifentanil	+	NSAIDs	–
Morphine	–	COX-2 inhibitors	–
Meperidine	–		

COX-2, cyclo-oxygenase-2; NSAIDs, non-steroidal anti-inflammatory drugs.
+, can be used; –, cannot be used; +/– could be used.

Neuromuscular blocking agents

Succinylcholine is frequently used in general anaesthesia to facilitate tracheal intubation because of its rapid onset and brief duration of action. However, it may increase serum potassium concentration, which can result in cardiac arrhythmias and even cardiac arrest (85). Patients with renal failure may have associated uraemic polyneuropathy, and repeated doses of succinylcholine can trigger hyperkalaemia in such patients (86). Therefore, succinylcholine should be used cautiously in patients with end-stage renal failure. Its use is not recommended in patients with end-stage renal failure who have concomitant hyperkalaemia.

Long-acting non-depolarizing neuromuscular blocking agents are largely eliminated by renal excretion. Hunter (87) found that, in patients with end-stage renal failure, the effects of long-acting non-depolarizing neuromuscular blocking agents were significantly prolonged, with a high rate of residual blockade at the end of surgery and a notable cumulative effect with repetitive administration. Therefore, in patients with ESRD, muscle relaxants whose excretion is not primarily dependent on renal function should be used for general anaesthesia.

The onset time of various muscle relaxants in patients with end-stage renal failure has been reported by different studies to be similar or prolonged when compared with controls (88, 89). A slower onset time may be seen in patients with water intoxication as a result of the increased volume of distribution, whereas a more rapid onset time may be observed in patients with dehydration caused by dialysis therapy as a result of a smaller volume of distribution.

The duration of action of muscle relaxants is dependent on the excretory route of the agents. Excretion of atracurium is via Hofmann elimination and hydrolysis by esterase, and hence renal failure does not alter its elimination. The duration of action and recovery time of initial and incremental doses of atracurium in patients with end-stage renal failure are similar to those in controls (90, 91). However, the metabolite of atracurium, laudanosine, is partially eliminated through the kidney, resulting in a prolonged elimination half-life of this metabolite in patients with renal failure (92). The concentration of laudanosine required to produce convulsions in dogs is more than 20 μg/ml; the concentrations found after the clinical use of atracurium are between 2 and 14 μg/ml.

Cisatracurium is approximately four times as potent as atracurium. Its principal mode of breakdown is also Hofmann elimination, and laudanosine is one of its breakdown products. There is no direct metabolism by esterases. As it is more potent, smaller amounts of cisatracurium are required, and therefore less laudanosine is formed. Even in patients with renal failure or those receiving prolonged infusions, the highest plasma levels of laudanosine are well below the toxic threshold, about one-fifth of the level found with atracurium. The duration of action is, however, slightly prolonged in renal disease, suggesting that it may normally undergo slightly more renal excretion than atracurium.

Mivacurium is eliminated by hydrolysis by plasma cholinesterase at a hydrolytic rate of 70–80% of that of succinylcholine. The proportion of elimination of mivacurium by the kidney is minimal. Cook et al. (93) found no significant difference in the pharmacokinetics or pharmacodynamics of mivacurium between patients with renal failure and controls, but others (94, 95) found that the no-response period of mivacurium was significantly prolonged in patients with end-stage renal failure, probably because of the decreased plasma cholinesterase activity in patients on long-term dialysis therapy.

The elimination of vecuronium and rocuronium is relatively independent of kidney function. Both drugs are mainly metabolized by the liver, but their metabolites and partial prototypes are excreted by the kidney. The duration of action of vecuronium and rocuronium in patients with renal failure has been reported to be prolonged (96–98), and a cumulative effect has been noted with repetitive administration (99, 100). This is caused by the accumulation of an active metabolite that is produced in the liver by the removal of the acetyl group. In a case report, a patient with chronic renal insufficiency had complete neuromuscular blockade for more than 3 h after an initial dose of 0.09 mg/kg vecuronium (100).

Ma and Zhuang (94) reported that, in patients undergoing dialysis 1 day before transplantation, no difference in the no-response period or the time to 25% recovery after an initial dose of vecuronium or rocuronium twice the ED95 (dose required to produce 95% suppression of twitch responce to nerve stimulation) value was noted when compared with controls. However, after repetitive incremental doses, the no-response period and the time to 25% recovery were prolonged. Renal failure leads to decreased plasma clearance and a prolonged elimination half-life of vecuronium and rocuronium, as discussed earlier. However, Khuenl-Brady et al. (101) found that neither the duration of action nor the recovery after an initial dose, or even three subsequent incremental doses, was prolonged in patients with chronic renal failure who were given rocuronium. Neuromuscular function can recover spontaneously without an antagonist after the use of rocuronium in patients with renal failure (97, 101).

Inhalational agents

All potent inhalational agents cause a decrease in the renal blood flow and glomerular filtration rate in proportion to the dose. The association between the metabolic production of inorganic fluoride ions and high-output renal failure has been known for years. Serum fluoride levels of 50 μmol/l are needed to produce nephrotoxicity, but significant decreases in the maximum urine-concentrating ability can occur when serum fluoride levels are on the order of 20 μmol/l.

Enflurane is metabolized to a small extent, and occasional cases of renal failure have been reported following its use. With enflurane, maximal serum fluoride levels are on the order of 25 μmol/l. It should not be used in patients with renal impairment. Although fluoride is also the major metabolite of isoflurane, the extent of its metabolism is so small (0.2%) that the amount of fluoride produced is unlikely to cause renal damage.

Sevoflurane is degraded to fluoromethyl-2,2-difluoro-1-trifluoromethyl vinyl ether (compound-A) by carbon dioxide absorbers of standard anaesthesia re-breathing systems. A decrease in fresh gas flow is known to increase compound-A production within the circuit, thereby increasing compound-A levels (102). Compound-A has been shown to be nephrotoxic in rats (103, 104). However, studies performed to assess the safety of sevoflurane in patients with pre-existing renal disease have reported that renal dysfunction is not enhanced by compound-A (105, 106).

Sevoflurane is metabolized by hepatic cytochrome P450 to hexafluoroisopropanol and inorganic fluoride. Peak serum inorganic fluoride levels greater than 30 μmol have been reported after sevoflurane anaesthesia (107, 108). Although such high levels of inorganic fluoride are known to produce transient renal damage after enflurane anaesthesia, a similar deterioration has not been found after sevoflurane anaesthesia, even in patients with pre-existing renal disease (105–108). Conzen et al. (109) did not find any correlation between serum inorganic fluoride and compound-A levels and the markers of renal function after low-flow sevoflurane anaesthesia in patients with co-existing renal disease.

Bito et al. (110) have demonstrated that low-flow sevoflurane anaesthesia does not cause renal injury when compared with high-flow sevoflurane or low-flow isoflurane anaesthesia. In their study, blood urea nitrogen and creatinine concentrations did not increase, and creatinine clearance did not decrease, when compared with values before anaesthesia, although there was an insignificant increase in the urinary excretion of the kidney-specific enzymes *N*-acetyl-β-D-glucosaminidase and alanine aminopeptidase. Similarly, Conzen et al. (109) reported that low-flow sevoflurane anaesthesia was safe and did not alter kidney function in patients with pre-existing renal disease. Hence, low-flow sevoflurane anaesthesia can be safely used in renal transplant recipients. Furthermore, sevoflurane has been shown to have an anti-inflammatory effect that protects against ischaemia–reperfusion injury (111). Lee et al. (112) demonstrated anti-inflammatory and anti-necrotic effects of sevoflurane in cultured kidney proximal tubule cells.

Similarly, desflurane is not contraindicated in patients with renal dysfunction (113, 114). Litz et al. (114) found no deterioration in renal function in patients with pre-existing renal disease who were given 2.2 ± 1.8 minimum alveolar concentration (MAC) hours of desflurane. In another study, Obal et al. (115) examined the effects of post-conditioning by desflurane on renal function and morphology in rats. Post-conditioning involves the administration of anaesthetics during early reperfusion, and has been found to have a protective effect on several organs. They administered 1 MAC of desflurane during post-conditioning and found that it protected renal function and tissue.

Induction agents and other drugs

Propofol is extensively used as an intravenous agent for the induction and maintenance of general anaesthesia. Propofol is mainly metabolized in the liver and its metabolites do not possess pharmacological activity (116). Studies have shown that propofol can be safely used for the induction and maintenance of anaesthesia in patients with renal failure (117, 118). Uraemia requiring HD has not been shown to affect significantly the pharmacokinetics of propofol. Infusion dose requirements have been found to be similar in ESRD patients and patients with normal renal function (118). Shorter emergence times have been noted in ESRD patients when compared with patients with normal renal function (118, 119). No adverse effects have been reported following intermittent injections of propofol.

Thiopental is another inducing agent that is almost entirely metabolized in the liver. Its breakdown products are excreted by the kidneys and the alimentary tract. Traces are excreted unchanged in the urine. No permanent effects of this agent on kidney function have been recorded.

The use of glycopyrronium is contraindicated in uraemic patients. Kirvela et al. (120) reported severe impairment of glycopyrronium elimination in uraemic patients undergoing renal transplantation. In their study, the 24-h renal excretion of glycopyrronium was 7% (0–25%) in uraemic patients and 65% (30–99%) in ASA I control patients undergoing general surgery.

Opioids

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 (121). Similarly, the administration of high or repeated doses of meperidine in these patients is known to produce seizures as a result of the accumulation of normeperidine (122). The elimination of oxycodone is also impaired in uraemic patients undergoing renal transplant. Kirvela et al. (123) reported a prolonged mean elimination half-life of oxycodone in patients with end-stage renal failure. They found higher concentrations of its metabolite noroxycodone in plasma. Furthermore, uraemic patients were found to excrete significantly smaller quantities of oxycodone and its metabolites, noroxycodone and oxymorphone. However, the pharmacokinetics of fentanyl, alfentanil and 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 accumulate.

Remifentanil is metabolized in the peripheral tissues by an esterase enzyme. Its principal metabolite, GR90291, possesses about 1/4600th the potency of remifentanil, and is eliminated primarily by the kidneys (124). Hoke et al. (125) studied the pharmacokinetics and pharmacodynamics of remifentanil in patients with chronic renal failure. In their study, blood pressure elevations were noted before and after the termination of remifentanil infusion in patients who had dialysis fistulae or grafts. Dialysis fistulae are known to produce hyperdynamic circulation. They also found that the adverse effects were mild and were the result of typical micro-opioid effects, including dyspnoea, somnolence, nausea, vomiting and chills. However, the maximum concentration and plasma half-life of GR90291 were markedly increased.

In another study, Bower and Sear (126) found no correlation between alfentanil binding and plasma

albumin, total plasma proteins, plasma urea or plasma creatinine clearance in patients with chronic renal failure. However, in these patients, total drug clearance and the volume of distribution were significantly increased.

Intravenous fluid therapy

Normal saline is routinely used for intra-operative intravenous fluid therapy in renal transplant recipients. Electrolyte imbalance, especially hyperkalaemia, is frequently seen in patients with renal failure. Potassium-containing fluids, such as lactated Ringer's solution, are thus avoided in such patients in order to minimize the risk of development of hyperkalaemia.

Metabolic acidosis has been reported to develop following the administration of large volumes of normal saline (127, 128). Various possible explanations for this metabolic derangement have been suggested. The rapid administration of fluids containing near-physiological concentrations of sodium and anions (other than bicarbonate) dilutes the extracellular bicarbonate, resulting in dilutional acidosis (129). Furthermore, normal saline could cause metabolic acidosis as a result of its chloride content, according to Kellum (130). He suggested that, although the proportion of sodium and chloride is similar in normal saline, it is not so in the plasma. Hence, the administration of large volumes of normal saline has a greater effect on total body chloride than on total body sodium, leading to the development of metabolic acidosis (130). Hyperchloraemic metabolic acidosis further leads to an extracellular potassium shift, producing hyperkalaemia (131).

Although normal saline may have a potential detrimental effect on renal function, as described, it is still commonly used in patients undergoing transplantation. O'Malley et al. (132) have shown that normal saline does not adversely affect renal function.

Colloids should only be considered in recipients with severe intravascular volume deficits who require high-volume restoration (133). Artificial colloids, such as gelatin and dextran, are known to adversely affect the kidney (134). Albumin is a normal endogenous colloid with a wide safety margin, and hence should be used. Furthermore, albumin also protects the kidney by scavenging reactive oxygen species and inhibiting apoptosis (134).

Hydroxyethyl starch (HES) solutions are being used instead of albumin. Medium molecular weight HES solutions have been found to have the lowest *in vivo* molecular weight above the threshold for renal elimination and are also easily degradable (135). Furthermore, they do not have adverse effects on the reticuloendothelial system or renal function, nor do they have bleeding complications. In one study, immediate renal function was found to be impaired in renal transplant recipients whose donors were infused with HES (136). However, another retrospective 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 recipient (137). Sufficient amounts of crystalloids should, however, be infused together with HES.

Central venous pressure (CVP)

In the immediate post-transplant period, CVP invariably declines despite positive fluid balance and vigorous fluid resuscitation. Various explanations have been offered for this phenomenon: hypovolaemia in chronic dialysis patients; vasodilatation from anaesthetic drugs; altered vascular permeability or response to factors liberated from the perfused kidney. Reperfusion is known to produce oxygen-derived free radicals (138). These produce tissue damage, resulting in increased vascular permeability and alterations in vascular tone. The redistribution of fluids in different compartments as a result of pre-existing vascular permeability may lead to a decrease in CVP. The excretion of NO synthase inhibitor by the transplanted kidneys, leading to increased NO levels, has also been implicated in the decrease in CVP (139). However, concomitant vasodilatation as a result of NO has not been noted in recipients.

Acute tubular necrosis has been reported to be lower in patients who are profoundly hydrated (140, 141). Hyperhydration is known to dilate the atria, leading to the release of atrial natriuretic peptide (142). It also leads to increased renal perfusion.

Ferris et al. (143) have shown a lack of correlation between the decrease in CVP and fluid balance. In their study, although the fluid balance of recipients correlated strongly with immediate post-operative function, no correlation was detected between the absolute value of CVP intra-operatively or the post-operative decrease in CVP and the incidence of acute tubular necrosis. Furthermore, they found that the maximum decrease in CVP occurred between the operating theatre and intensive care unit. This could be the result of the prompt redistribution of fluids, or the fact that patients with ESRD have a different post-anaesthetic response.

Anaesthesia procedure

Adequate monitoring is a prerequisite for renal transplantation. A central venous line is essential

for the assessment of volume status. Intra-arterial blood pressure monitoring is useful for patients with significant cardiovascular disease.

Both epidural anaesthesia and general anaesthesia are used for providing anaesthesia during renal transplantation. Haemodynamics and renal function have not been reported to differ significantly in the two techniques (144). Dahaba et al. (145) found no difference in haemodynamic responses to perioperative events and recovery parameters when using total intravenous anaesthesia with remifentanil, propofol and cisatracurium in patients with end-stage renal failure and those with normal renal function. Kirvela et al. (146) found no advantage of using total intravenous anaesthesia with propofol and alfentanil over balanced anaesthesia with isoflurane–nitrous oxide–fentanyl.

Post-operative pain relief

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. Morphine or fentanyl delivered by patient-controlled analgesia is known to provide sufficient pain relief. Post-operative epidural analgesia has been found to be more effective than intravenous tramadol (144). However, the use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided. Martin et al. (147) demonstrated an altered disposition of paracetamol in renal transplant recipients. The clearance of paracetamol from plasma and the renal elimination of its glucuronide and sulphate conjugates were prolonged. Furthermore, the elimination of its conjugates was found to correlate negatively with serum creatinine levels. 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 (148). Cyclo-oxygenase-2 enzyme inhibitors have also been reported to be nephrotoxic in transplant recipients and in patients with impaired renal function (149).

Conclusions

Kidney transplantation is the preferred treatment modality for patients with ESRD. A successful outcome after transplant is influenced by appropriate pre-operative assessment and drug treatment, close intra-operative monitoring, optimization of intravascular fluid volume and the appropriate use of anaesthetic agents.

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