Anaesthesia for renal transplantation

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Key points

Patients with end-stage renal failure often have significant co-morbidity

Ensure that the patient is optimally prepared for surgery and anaesthesia

Consider the effects of renal failure on drug handling

The CVP must be >10 mmHg (or PA diastolic pressure > 15 mmHg) to optimise the chances of early graft function

Hypotension or hypovolaemia threaten the newly grafted kidney with acute tubular necrosis

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Renal transplantation was first attempted in 1906, and since the introduction of chemical immunosuppression in the 1960s it has become the preferred treatment for end stage renal failure. In 1999, approximately 1600 kidney transplants were performed in the UK. Two-year graft survival is now over 80% for cadaveric and 90% for living-donor grafts, and overall patient survival is in excess of 95%. As kidney transplantation has become more successful, the criteria for patient selection have been relaxed. Most patients receiving dialysis are now candidates for transplantation, including the elderly, and those with significant medical co-morbidity. A successful transplant results in improved quality of life and prolonged survival. However, demand for transplant kidneys exceeds supply. Performing a transplant in a high-risk patient may be appropriate, if they accept the increased risk; the anaesthetist plays a crucial role in the success or failure of this challenging operation.

Pre-operative considerations

Major contra-indications to renal transplantation include active malignancy or infection, severe vascular disease, recent myocardial infarction and end-stage disease in other systems. Many conditions previously considered to be absolute contra-indications are now only relative contra-indications, such as obesity (BMI >30 kg m^{-2}), sickle-cell disease, old age, poorly controlled diabetes, and primary renal disease with a high recurrence rate in the transplanted kidney. Surgery may be considered in patients with diffuse coronary artery disease providing ventricular function is adequate. The process of patient selection should allow for anaesthetic input, particularly regarding their cardiovascular and respiratory status for anaesthesia, and previous anaesthetic-related problems.

Some important causes of end-stage renal failure (ESRF) are listed in Table 1. Diabetes mellitus is the most common, and is associated with increased pre-operative ST segment changes and pulmonary congestion, and higher death rates after kidney transplant. ESRF has many systemic effects (Table 2).

Table 1 Some important causes of chronic renal failure

Diabetes mellitus	44%
Other glomerulonephritis	23%
Polycystic kidney disease	6%
Chronic pyelonephritis	5%
Systemic lupus erythematosis	
Alport's syndrome	
Arterial disease (hypertension, atherosclerosis)	
Unknown	7–15%

Organs are obtained from living-related donors, brain-stem dead donors, and non-heart beat cadaveric donors. Living-related kidney transplantation is an elective procedure with excellent graft survival of over 90% even for HLA incompatible subjects. The donor's mortality is less than 0.1%, and their 5-year life expectancy is normal. However, only a minority of patients with renal failure can identify a suitable living-related donor, and most transplants are performed with cadaveric organs. Graft survival is over 80% at 1 year and 70% at 3 years; priority is given to cases of clinical urgency.

Cross-matching involves ABO compatibility, HLA matching, and testing donor T cells against stored recipient serum. ABO compatibility is essential, and kidneys are usually transplanted within blood groups to prevent discrimination against potential recipients with blood group O. HLA matching is undertaken at the three important loci – A, B and DR – for which there are a total of six possible antigens. If all six match the donor kidney (a 'full-house' match), the success rates are excellent, and the tendency to reject low. However, strict application of these criteria limits the number of transplants performed, and can exclude potential recipients who have a less than perfect match. Therefore, many kidneys are

Table 2 Effects of end-stage renal failure

System	Effects
Cardiovascular	Hypertension (up to 80%)
	Accelerated atherosclerosis
	Ischaemic heart disease (25%)
	Left ventricular failure
	Uraemic cardiomyopathy
	Cerebrovascular accidents
	Hyperlipidaemias
Respiratory	Pulmonary oedema
	Pleural effusions
	Increased chest infections
Nervous	Peripheral neuropathies
	Autonomic neuropathies
	Mental changes: lassitude, depression, psychosis, coma
Haematological	Anaemia (Hb 6–8 g dl^{-1} without erythropoietin treatment)
	2,3-DPG increased, oxyhaemoglobin dissociation curve shifted to right
	Platelet count decreased
	Platelet activity decreased
Musculoskeletal	Osteodystrophy (fractures, soft tissue calcification, deformities, pruritis)
	Muscular weakness
Gastrointestinal	Peptic ulceration
	Nausea and vomiting

transplanted with lower degrees of HLA matching, though this is controversial. CMV status is less important with the availability of modern anti-viral agents.

Pre-operative preparation

When an organ becomes available, the potential recipient is reviewed promptly by the nephrologist, transplant surgeon and anaesthetist to allow adequate preparation, or, in extreme cases, the selection of an alternative recipient. Any new evidence of cardiovascular disease, infection and other illness must be sought. Essential basic investigations comprise haemoglobin, urea and electrolytes, electrocardiogram and chest X-ray. Depending on fluid balance and metabolic status, patients are dialysed pre-operatively to within 0.5 kg of ideal body weight; hyperkalaemia and acid-base abnormalities are corrected. Hypovolaemia must be avoided, as hypotension increases the possibility of acute tubular necrosis in the transplant. With routine pre-operative dialysis, mortality has reduced from 16% to less than 1% in most recent series.

Before the availability of recombinant erythropoietin (EPO), marked chronic anaemia was common, and patients often required peri-operative blood transfusion. EPO treatment is used to maintain Hb at 9.5 g dl^{-1}, to reduce fatigue and depression and improve exercise tolerance. However, EPO may worsen hypertension, and lead to increased clotting of vascular access sites. Modern immunosuppressive agents preclude any benefit from pre-graft transfusion before transplantation as a means of promoting graft survival. Blood should be available for theatre, but transfused only if necessary. Uraemia results in a prolonged bleeding time, due to a low platelet count and reduced platelet function. Prothrombin time and partial thromboplastin times are usually normal, but anticoagulation from dialysis should be reversed before surgery.

Delayed gastric emptying is common, caused by diabetes, autonomic neuropathy and anxiety. An H_2 receptor antagonist, metoclopramide, or sodium citrate may be administered pre-operatively, but a rapid sequence induction may be indicated. Patients are often anxious, and the anaesthetist should take time to establish a rapport, and explain the procedure. Anxiolytic premedication, *e.g.* temazepam, may be required. In addition, the surgical team will have prescribed immunosuppressive drugs. The mainstay of therapy is usually cyclosporin, azothiaprine and glucocorticoids, although variant regimens exist. Methyl-prednisolone is often given intravenously on induction of anaesthesia. Immunosuppressant drugs have many adverse effects, but in particular the monoclonal antibody against T cells, muromonab CD3 (OKT3), has caused pulmonary oedema and fits.

Surgical procedure

At operation, an appropriate site for the renal allograft is chosen (the right iliac fossa is generally preferred if no contraindication is present). The abdominal wall muscles are divided to expose the bladder and iliac vessels. The cooled, flushed kidney is then brought to the patient, and positioned where it lies most naturally. The deeper venous anastomosis is usually performed first, followed by the arterial anastomosis. The anastomosis time should be as short as possible, and is usually about 35 min. The vascular clamps are then removed. This is a critical time for the anaesthetist (see below). After this, the ureteric anastomosis is made, usually directly to the bladder, which is distended with antibiotic containing fluid. Variations on the arterial and ureteric anastomoses may be necessary.

Anaesthetic technique

Regional or general anaesthesia?

Regional anaesthesia has been successfully used for kidney transplantation. However, the procedure can be prolonged (>2.5 h) and central venous catheter insertion may distress the patient. The risks of neurological complications may be compounded by impaired blood clotting, and regional techniques may complicate assessment of intravascular volume. Problems with fluid preloading for regional anaesthesia have been described frequently,

(including cardiac arrest), and over 40% (and up to 95% in one series) of patients may require conversion to general anaesthesia. Therefore, general anaesthesia is usually considered the technique of choice.

Positioning and monitoring

Arterio-venous fistulas must be protected, and blood pressure cuffs, and venous and arterial lines must be sited on the opposite arm. The fistula should be wrapped in padding and palpated at intervals to ensure continued patency; the surgeon should be informed immediately if patency is lost. Routine monitoring (ECG with ST segment monitoring is preferable), should commence before anaesthesia is induced. Neuromuscular and temperature monitoring should be used. Hypothermia leads to vasoconstriction, increased bleeding, and fluid management is complicated during the re-warming period. The patient should be kept normothermic using forced air warmers and warmed intravenous fluids as required.

Central venous pressure monitoring is essential to guide assessment of intravascular volume, though patients who have had dialysis through central venous lines may have stenosis of central veins. A triple lumen catheter allows additional access for the administration of dopamine and other drugs. Pulmonary artery catheter monitoring and invasive arterial blood pressure monitoring may be required in patients with severe cardiovascular disease.

Induction and maintenance of anaesthesia

The patient's airway should be protected with an endotracheal tube, as uraemic patients are at risk of aspiration. Pre-oxygenation should be performed, and a rapid sequence induction may be indicated (suspected incomplete gastric emptying from any cause especially if there is a history of GI reflux, diabetes, or autonomic neuropathy). Anaesthesia may be induced slowly with propofol, thiopentone or etomidate, whilst monitoring haemodynamic parameters, and titrated to effect if a rapid sequence technique is not required. Propofol has been successfully used for total intravenous anaesthesia for kidney transplant surgery, and was associated with a reduction in postoperative nausea and vomiting. Suxamethonium in intubating dose causes a rise in serum potassium averaging 0.5 mmol l^{-1}, (maximum of 0.7 mmol l^{-1}) in patients with renal failure. Cardiac arrest and death have been reported in patients with pre-existing hyperkalaemia, and in those given repeated doses. It should not be administered to patients with serum potassium concentrations >5.5 mmol l^{-1}, or those with uraemic neuropathies. Under these circumstances we modify any rapid sequence induction technique to avoid its use. Because most of these patients are hypertensive, intravenous opioids (*e.g.* alfentanil, 10–15 mcg kg^{-1}) may be used to blunt the stress response to laryngoscopy and tracheal intubation.

Non-depolarising relaxants (such as atracurium, *cis*-atracurium, vecuronium or rocuronium) are suitable as their excretion is independent of the kidney. Atracurium has theoretical advantages as it is also broken down by Hofmann degradation. Pancuronium is best avoided as its action may be prolonged, 80% being eliminated through the kidneys.

Isoflurane may be the inhalational agent of choice as only 0.2% is metabolised, it produces low levels of inorganic fluoride ions, and causes few cardiac arrhythmias. It may also have less effects on cardiac output and renal blood flow than other agents. Enflurane has been used without untoward effects on graft function, but fluoride levels approach 75% of nephrotoxic levels, and it is not recommended. Halothane has been used extensively, but its arrhythmogenic potential may be enhanced in these patients. There are few published data relating to the newer volatile agents in patients undergoing renal transplantation.

Fentanyl may be used in normal doses, as excretion is mainly by hepatic metabolism. Morphine can caused prolonged effects, *e.g.* sedation and respiratory depression in renal failure, because the active metabolite, morphine-6-glucuronide, accumulates. It should be titrated carefully, and prolonged effects should be anticipated for a given dose. Pethidine has no particular advantages in these patients, and norpethidine can accumulate.

Management goals during renal transplant surgery

During routine surgery in patients with co-existing renal failure, intravenous fluids are often minimised, to prevent fluid overload and reduce the need for postoperative dialysis. Kidney transplantation is an important exception to this rule. When the vascular clamps are removed, good perfusion of the new kidney is essential to give the best chance of immediate function; this is dependent on adequate intravascular volume and the avoidance of hypotension. The target central venous pressure should be ≥10–12 mmHg, or if a pulmonary artery catheter is *in situ*, the diastolic pulmonary artery pressure should be ≥15 mmHg. Below these values, there is an increased incidence of acute tubular necrosis in the grafted kidney. However, a surprising volume of fluid may be required to achieving these targets. In some studies, typical volumes were 60–100 ml kg^{-1}, emphasising the need for central venous monitoring. The type of intravenous fluid used is less important. Normal (0.9%) saline is a logical choice, as it is high in sodium, (particularly important if mannitol is used, see

below), and contains no potassium or lactate. Albumin and colloids have also been advocated. Blood should be transfused if required. Intra-operative blood loss is usually less than 500 ml, but the possibility of sudden massive haemorrhage is present (8000 ml has been reported). Sometimes release of the vascular clamps will result in significant blood loss, which must be replaced promptly to maintain perfusion of the new kidney.

The anaesthetist may be asked to administer diuretic drugs to promote immediate function of the transplanted kidney, and to increase urine production. Mannitol, an osmotic diuretic, is often used in doses of 20–50 g. It may result in a rise in serum potassium level exceeding 1 mmol l^{-1}, and may also cause a profound reduction in serum sodium level in patients with renal failure. Frusemide (in doses of 200–500 mg) has also been used to promote urine flow. Dopamine is often used for two purposes. There are theoretical grounds for its use as a DA_2-receptor agonist (in doses of 2–3 mcg kg^{-1} min^{-1}) to promote renal blood flow. However, no outcome benefit has been proven, possibly due to cyclosporin-induced vasoconstriction. At doses of 5–10 mcg kg^{-1} min^{-1}, β-adrenergic effects can help in maintaining normotension. At higher doses, α-adrenergic effects of dopamine predominate, and blood flow to the grafted kidney may actually be reduced. This should be avoided. Similarly, the α-adrenergic agonists, methoxamine and phenylephrine, cause a large reduction in renal blood flow to a transplanted kidney, and are best avoided. If hypotension is a problem despite adequate filling, β-agonists such as dobutamine or dopexamine are preferable.

In summary, the anaesthetist has a crucial role regarding the successful early function of the transplanted kidney. The goal is a full circulation and normotension when the vascular clamps are released. This will require CVP monitoring, adequate (and sometimes surprising) fluid volumes, and a good dialogue with the surgeon to predict problems before they arise.

Postoperative care

Close monitoring of the patient is required after surgery, with particular attention to fluid balance. Supplemental oxygen should be administered, and provision for additional postoperative analgesia made. Arterial and central venous pressures should be monitored and fluids titrated judiciously, to ensure that the graft is not threatened by hypotension or hypovolaemia. Urine output must be monitored constantly; a sudden decrease may indicate problems with the anastomosis, requiring surgical re-exploration. Early graft function is the norm in transplants from living related donors, and is achieved in 70% of cadaveric transplants. However, the postoperative fluid regimen must allow for the possibility that graft function is delayed. Hypovolaemia must be avoided, as this will further threaten graft function, and isotonic 0.9% saline at 30 ml h^{-1} plus the previous hour's urine output is usually appropriate. It should be adjusted according to blood results. Additional fluids may be required to maintain the CVP, which may fall as a result of third-spacing of fluids, blood loss, or vasodilation associated with re-warming if the patient has become hypothermic. Hyponatraemia and hyperkalaemia may occur associated with mannitol. Blood should be transfused if necessary. A chest X-ray will confirm the position of the central line or pulmonary artery catheter, and allow inspection of the pulmonary vasculature and lung fields.

Epidural analgesia has been used successfully for postoperative analgesia for kidney transplantation. However, hypotension must be avoided, and careful fluid balance maintained. If opioids are used, active metabolites of morphine may accumulate, as immediate function of the new kidney is not guaranteed. Repeat doses should be reduced accordingly, and the dosing interval increased. Patient-controlled analgesia (PCA) may be used with care. We reduce the dose of PCA morphine (*e.g.* 0.5 mg boluses with a 10 min lock-out period). The effect must be monitored, and the dose and interval adjusted if necessary. The site of the incision appears to lend itself to intercostal nerve blocks. Unfortunately, there is a significant incidence of pneumothorax, and their effect is only short-lived. A postoperative chest X-ray is mandatory. Non-steroidal anti-inflammatory drugs should be avoided at all costs, as they reduce renal blood flow and may threaten the new kidney.

Summary

Anaesthesia for kidney transplantation is challenging, and yet mortality remains low. The technique chosen will be pragmatic, based on a sound knowledge of underlying principles. However, optimisation of volume status and blood pressure are fundamental to the early success of the transplanted kidney.

Key references

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See multiple-choice questions 13–16.