Anaesthesia for renal transplant surgery: an update

Sebastian Schmid and Bettina Jungwirth

Although the overall outcome of patients undergoing renal transplant surgery has improved in recent years, delayed graft function and myocardial infarction remain common and severe postoperative complications. This review article provides an update on anaesthesia for renal transplant surgery in order to optimise perioperative therapy and improve the outcome of these patients. In particular, the characteristics of this high-risk population and the recommendations for preoperative ‘work-up’ are summarised. Care for the living donor, commonly used drugs and their potential nephrotoxic properties are discussed. Finally, the current knowledge about volume therapy, optimised haemodynamic management and postoperative care is described.

Introduction

In 1954, Guild et al. performed the first successful renal transplantation on identical twins. In recent years the organ survival rate has increased significantly, mainly due to improvements in immunosuppressant therapy. Many studies have shown a significant reduction of mortality in patients following renal transplantation compared with patients remaining on the waiting list. Therefore, the kidney donor pool, as well as the number of recipients, has been expanded, including donors as well as recipients older than 60 years, and the use of marginal organs for transplantation.

Despite this substantial progress in renal transplant surgery, the risk of perioperative complications remains. About 25% of all kidney recipients suffer from postoperative delayed graft function, needing renal replacement therapy, resulting in an increase in mortality of 40%. Cardiovascular complications have been described in 10% of renal transplant recipients, particularly in patients older than 50 years. Perioperative caregivers, including anaesthesiologists, need to optimise the treatment of these high-risk patients in order to reduce postoperative complications. In particular, anaesthesiologists require a consolidated knowledge of the characteristics of renal transplant patients and of the impact of their co-morbidities on outcome. Optimised haemodynamic management and the identification and avoidance of potentially nephrotoxic drugs are essential.

This review provides an update on recommended preoperative assessment, care for the living donor, the use of potential nephrotoxic drugs and haemodynamic and postoperative management in renal transplant surgery patients.

Preoperative assessment

Patients undergoing renal transplant surgery present with several risk factors which have an impact on postoperative outcome (Table 1). These factors should be identified during an extensive preoperative ‘work-up’, not just for risk stratification but also for the development of a tailored perioperative treatment regime including advanced haemodynamic monitoring. Cardiovascular disease remains the most important limiting factor affecting postoperative morbidity and mortality. The incidence of coronary artery disease in patients with chronic kidney disease is 25%. According to the ACC/AHA perioperative guidelines, patients who need emergency surgery, such as those undergoing renal transplant surgery, ‘should proceed to the operating room and the attending anaesthetist has to continue perioperative factor management’. As patients are on the waiting list for some years before a suitable donor organ is available, repeated cardiac assessment is recommended, particularly in patients with active cardiac conditions such as unstable coronary syndromes, decompensated heart failure, significant arrhythmias and severe valvular disease.

Other co-morbidities often associated with chronic kidney disease include hypertension and diabetes mellitus. The prevalence of hypertension is up to 90% in patients with a glomerular filtration rate below 30 ml/min. Hypertension is both a cause and a consequence of chronic kidney disease. The latter is mediated via different mechanisms including activation of the renin–angiotensin–aldosterone system and fluid overload. Diabetes mellitus is seen in up to 30% of patients who need renal replacement therapy and can aggravate hypertension and cardiovascular disease, resulting in a greater risk of stroke or myocardial infarction. According to the recent ESA guidelines on perioperative cardiac evaluation, renal transplantation is an intermediate-risk surgical procedure. Because end-stage renal disease is a risk factor for cardiac complications, a 12-lead ECG is recommended and low-dose β-blocker therapy.
is recommended. As the medication should be started at least 1 week before surgery, initiation of therapy has to be considered when adding the patient to the transplant list.\textsuperscript{19}

The immediate preoperative assessment includes identification of disturbances in acid–base balance and electrolytes, as well as an estimation of fluid status, which can range from severe hypovolaemia to pronounced hypervolaemia in patients undergoing renal transplant surgery. The patient’s volume status can be estimated by the frequency of dialysis and when it was last performed. Several studies have investigated the benefit of dialysis immediately prior to surgery. Although one study showed no benefit in relation to delayed graft failure or 1-year survival, another larger retrospective study (more than 22,000 patients) demonstrated a greater risk of delayed graft failure in patients on haemodialysis compared with patients on peritoneal dialysis, who usually present with a better volume status.\textsuperscript{20,21} Although further studies are needed, the routine use of haemodialysis immediately prior to surgery cannot be recommended, but should be considered in patients with high serum potassium levels which may be accentuated during graft reperfusion when a significant amount of potassium is released. Most patients have a dialysis shunt in place which requires special care during positioning for surgery. Its cannulation is reserved for absolute emergencies such as resuscitation without other vascular access. Metabolic acidosis is a common problem in patients with end-stage renal disease. Careful correction of acidosis during surgery is recommended for two reasons. First, adjustment of acid–base balance with bicarbonate helps to reduce the commonly elevated levels of serum potassium. Second, the function of the transplanted kidney is supported, particularly in terms of maintaining a balanced acid–base state.\textsuperscript{22} Blood glucose concentration should be managed; a level more than 8.9 mmol/L during reperfusion is associated with delayed graft function after surgery.\textsuperscript{23}

Living donor transplantation

Living donor transplantation has become more common due to the shortage of organs. The European organisation responsible for the allocation of organs (Eurotransplant) has reported a 30% increase in the number of living donor transplants in the last 5 years.\textsuperscript{24} Patients receiving organs from a living donor are usually in a better clinical condition. In some patients, pre-emptive kidney transplantation is performed before they require renal replacement therapy and develop complications associated with dialysis.\textsuperscript{25} This leads to a better postoperative outcome, with an increased 5-year graft survival (80% vs. 69%) compared with deceased donor transplantation.\textsuperscript{26} Survival, as well as the incidence of end-stage renal disease, in patients who donate a kidney is similar to the normal population, and donors have no long-term disadvantage.\textsuperscript{27} Nephrectomy can be performed as an open or laparoscopic operation with no difference in postoperative kidney function, but with more severe pain after open surgery.\textsuperscript{28,29} A combination of general and epidural anaesthesia should be considered, as the avoidance of pain is of paramount importance. The optimal volume management (type and amount of fluid) is still under debate. Starting hydration on the evening before surgery can increase postoperative urine output of the transplanted patient, without any effect on organ function after 3 days.\textsuperscript{30}

Avoidance of potentially nephrotoxic agents

Potential nephrotoxic agents should be avoided in any patient, but particularly in patients undergoing renal transplant surgery and in potential kidney donors. The nephrotoxic properties of drugs commonly used during anaesthesia warrant special consideration in this review and are summarised in Table 2.

Volatile anaesthetics

There have been some safety concerns about the use of sevoflurane for renal transplant surgery. Compound A is generated as a result of a chemical reaction between sevoflurane and the carbon dioxide absorbent. There is evidence that Compound A harms renal function in rats\textsuperscript{11,32}; however, this effect has never been shown in humans. In contrast, many studies have shown no negative effect on renal function.\textsuperscript{33–35} and sevoflurane can be used safely for renal transplant surgery, as can isoflurane and desflurane.\textsuperscript{36} Due to fluoride ions from the metabolism of enflurane, some cases of kidney failure have

<table>
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<th>Risk factors</th>
<th>Ischaemic heart disease</th>
<th>Diabetes mellitus</th>
<th>Arterial hypertension</th>
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| Preoperative 'work-up' | 12-lead ECG              | Electrolytes, coagulation studies, full blood count | Assessment of fluid status (last dialysis, residual excretion) |

| Table 1 Preoperative assessment of patients undergoing renal transplant surgery
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| Table 2 Suitability of drugs commonly used during renal transplantation surgery
<table>
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<th>Use</th>
<th>Avoid</th>
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<tr>
<td>Volatile anaesthetics</td>
<td>Sevoflurane</td>
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<tr>
<td>Isoflurane</td>
<td>Desflurane</td>
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<tr>
<td>Neuromuscular blocking drug</td>
<td>Cis-atracurium</td>
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<td>Atracurium</td>
<td>Sugammadex</td>
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<tr>
<td>Rapid sequence induction</td>
<td>Rocuronium 1.2 mg/kg</td>
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<tr>
<td>Opioids</td>
<td>Alfentanil analogues</td>
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<tr>
<td>Intravenous induction agents</td>
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<td>Thiopental</td>
<td>Etidronic</td>
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<td>Diuretics</td>
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been reported associated with the use of this volatile anaesthetic,\textsuperscript{37} and it should not be the first choice in patients undergoing renal transplant surgery.\textsuperscript{38}

**Neuromuscular blocking drugs**

The bowel motility in patients with end-stage renal disease may be reduced due to uraemic neuropathy. Although this could not be confirmed in large studies, some investigations have shown prolonged gastric emptying in patients with end-stage renal disease and diabetes.\textsuperscript{39,40} Therefore, a rapid sequence induction can be performed in order to reduce the risk of aspiration in diabetic patients, but it is not recommended for every patient undergoing transplantation. Succinylcholine can be used for rapid sequence induction bearing in mind that an increase in serum potassium concentration, particularly in patients with uraemic or diabetic neuropathy, may affect cardiac function.\textsuperscript{41} This has to be considered in patients with elevated serum potassium levels prior to induction or other co-morbidities that could cause a significant release of potassium due to up-regulated acetylcholine receptors, for example denervation.\textsuperscript{42} Rocuronium is an equally effective, non-depolarising, alternative when used at a dose of 1.2 mg.kg.\textsuperscript{43} However, prolonged neuromuscular blockade in patients with end-stage renal disease has been reported, especially when repetitive doses are used.\textsuperscript{44,45} Recently, sugammadex has been introduced for reversal of rocuronium-induced neuromuscular blockade. Due to the 100% renal excretion pathway of the sugammadex and rocuronium complex, its use is not recommended in patients with end-stage renal disease.\textsuperscript{45} The first clinical studies in patients on dialysis showed the efficacy of sugammadex was not impaired and there were no signs of reappearance of neuromuscular block.\textsuperscript{46} However, further studies are needed before sugammadex can be recommended in these patients.

If a rapid sequence induction is not necessary, non-depolarising muscle relaxants can be used. Atracurium and cis-atracurium are recommended as they are inactivated by Hofmann elimination and hydrolysis by esterases independent of renal function. Although the degradation products are eliminated renally, studies have shown muscle relaxation was not prolonged.\textsuperscript{47–49} Hofmann elimination is influenced, however, by blood pH. Acidosis is a common finding in end-stage kidney disease and may prolong the effects of atracurium and cis-atracurium. Laudanosine is a potentially toxic metabolite and undergoes renal elimination. At high concentrations it can cause convulsions. Although concentrations at toxic levels have never been seen in humans, cis-atracurium may be a safer choice, as it is about four times as potent as atracurium resulting in lower laudanosine levels.\textsuperscript{50,51} Mivacurium can also be used in renal transplant surgery. However, muscle relaxation may be prolonged due to decreased plasma cholinesterase concentration in patients with end-stage renal disease.\textsuperscript{52} Due to its long duration of action and potential to accumulate, pancuronium cannot be recommended. Neuromuscular monitoring is recommended in all patients undergoing renal transplant surgery.

**Induction agents**

Propofol and thiopental are safe for induction of anaesthesia in renal transplant surgery, as they are inactivated in the liver. The use of etomidate cannot be recommended as it induces adrenal insufficiency and increases mortality in critically ill patients.\textsuperscript{53}

**Opioids**

Morphine-6-glucuronide is an active degradation product of morphine and concentrations may be increased in patients with renal insufficiency. Therefore, morphine should be avoided for pain therapy in renal transplant surgery. In contrast, all the fentanyl analogues (including alfentanil, sufentanil and remifentanil) can be used safely.\textsuperscript{54}

**Diuretics**

The use of furosemide for the treatment of acute renal failure is controversial. Two large randomised controlled trials did not show any benefit of furosemide on the recovery from renal failure in patients with oliguria.\textsuperscript{55,56} The effect of diuretics on renal function after transplantation requires further study. The administration of 200 to 250 ml of mannitol 20% immediately before reperfusion has been shown to improve renal perfusion pressure. Three randomised controlled trials showed a significant, albeit transient, reduction in acute renal failure immediately after transplantation using mannitol\textsuperscript{57–59} and it is administered to nearly all patients undergoing renal transplant surgery.

**Haemodynamic management**

**Monitoring**

Advanced monitoring may optimise haemodynamic management and improve cardiac and renal outcome. However, the choice of monitoring device is still under discussion (Table 3).

**Central venous pressure**

Although some centres routinely use central venous pressure (CVP) to guide volume therapy, others use a central venous catheter in only 30% of renal transplant patients.\textsuperscript{60} This reflects the on-going debate on the use of CVP as suitable monitoring for optimising haemodynamic management. It has been shown that CVP does not correlate well with fluid status in general.\textsuperscript{61} This was also demonstrated in renal transplant patients.\textsuperscript{62} In contrast, other studies have shown a benefit of CVP-guided fluid therapy in these patients.\textsuperscript{63,64} The ideal range for the CVP has not been clearly identified. Some studies suggest slight over-hydration, others have shown no
increase in the incidence of delayed graft function with a more restrictive hydration regime (CVP 7 to 9 mmHg). In summary, it is not possible to provide a clear recommendation for, or against, the use of CVP in renal transplantation.

**Advanced haemodynamic monitoring**

Whether thermodilution or pulse contour-based devices such as the PiCCO (PULSION Medical Systems SE, Feldkirchen, Germany) or LiDCO (LiDCO Ltd, Cambridge, UK) can improve outcome after renal transplant surgery has not been studied. However, one limitation to the use of these devices is the need for an arterial line. Many of these patients have vascular disease and non-invasive devices, such as a recently introduced technique which computes beat-to-beat cardiac output from radial artery pressure and capillary pulse, could be an alternative. The use of transoesophageal or transthoracic echocardiography to assess fluid status during renal transplant surgery has not yet been studied. However, in some patients with significant cardiac complications or valvular disorders, echocardiography may be useful.

**Fluid therapy**

The management of fluid therapy depends on several factors. First, in the future, advanced haemodynamic monitoring may help to optimise the amount of fluid administered. Second, if the patient has some residual urine production, urine loss has to be replaced during surgery. A urinary catheter is needed and the urine output should be monitored. The exact timing of fluid therapy is controversial, but it seems sensible to administer the fluids evenly throughout surgery, rather than administering a bolus directly before reperfusion. The debate about the type of fluid to be used in renal transplant patients is on-going.

**Crystalloids**

In a survey performed in 2002, isotonic saline was used in more than 90% of renal transplant surgery procedures in order to avoid hyperkalaemia. However, recent studies have shown that its use leads to a significant increase of serum potassium when compared with Ringer’s solution. This effect is most likely due to an extracellular shift of potassium, caused by acute changes in blood hydrogen ion concentration which occurs in association with hyperchloraemic metabolic acidosis. Another study reported no difference in the change of serum potassium, although use of 0.9% saline leads to a significant decrease in pH and a significant increase in serum chloride. Modern balanced crystalloid solutions are inexpensive and seem to be a suitable hydration solution in renal transplant surgery. As larger volumes may be required and patients should be kept normothermic, fluids are warmed before administration. Although the risk of a significant increase in serum potassium is small, continuous monitoring of serum electrolytes is essential during the operation, especially just before and after reperfusion of the transplanted organ.

**Colloids**

Although there is little evidence from clinical studies for the use of albumin, many authors suggest an improvement in short-term and long-term outcome in renal transplant surgery patients after volume expansion with human albumin. These results were not confirmed in other investigations. Due to side-effects such as anaphylactic reactions and potential contamination with infectious diseases, the routine use of albumin is not recommended in renal transplant surgery. Artificial colloids such as gelatine, dextrans and hydroxyethyl starch (HES) have been developed within the last few years. Adverse effects have been reported with all of them. One problem is anaphylactic reactions which are more common with dextrans and gelatine than for HES. Other side-effects include bleeding complications, reticuloendothelial system dysfunction and impaired renal function. An ideal HES solution combines the lowest in-vivo molecular weight above the threshold for renal elimination, with a low degree of hydroxyethyl substitution. The data on the use of HES 6% 200/0.625 are inconsistent. Although the administration to non-living kidney donors resulted in a negative effect of HES on renal function, the data were not confirmed in other studies. In recent studies, medium molecular weight HES with a low molar substitution (HES 130/0.4) was shown not to affect the incidence of delayed graft function. In contrast to gelatine 4%, medium molecular weight HES shows a slight advantage regarding the recovery of renal function immediately after transplantation. However, concerns about the use of HES were highlighted by the VISEP trial which reported a higher incidence of renal failure in septic patients when high molecular HES was used in doses greater than the recommended daily maximum dose. Even though these findings cannot be easily translated to the setting...
of renal transplant surgery, the HES should be used with caution and reserved for special indications, such as the need for large volumes of fluid or for an increase in colloid osmotic pressure, until more data about the effect of medium molecular weight HES on graft function is available.

Further prospective randomised trials are required to identify the ideal fluid for renal transplant surgery and to assess whether the incidence of delayed graft function can be reduced by an optimised volume therapy regime.

Blood transfusion
Although the immunomodulatory effects of blood transfusion were used in the 1970s to reduce organ rejection, later investigations showed a higher incidence of acute graft rejection. As many patients undergoing renal transplant surgery are treated with erythropoietin, haemoglobin values are increased and blood transfusion is not required before the operation. As most patients have become accustomed to anaemia for some years and significant blood loss during the operation is rare, transfusion should be performed reluctantly; the transfusion trigger for these patients is not known, but is probably lower than in patients without renal failure.

Vasoactive agents
Next to the coronary and cerebral circulation, the transplanted organ benefits from optimised perfusion pressure, even though the ideal perfusion pressure during reperfusion is not known yet. However, improved oxygenation of the graft immediately after reperfusion results in decreased incidence of delayed graft function.

Dopamine
Dopamine has been used for many years for treatment of renal failure. However, two large meta-analyses have shown a detrimental effect of dopamine on renal function in acute renal failure. In addition, another study showed a higher mortality and prolonged length of ICU stay in patients receiving dopamine after renal transplant surgery. Therefore, the use of dopamine in renal transplant surgery cannot be recommended.

Dobutamine
In contrast, dobutamine can be used as a positive inotrope for patients with a low cardiac output. However, in these patients advanced haemodynamic monitoring may help to optimise volume and drug therapy.

Vasopressors
Optimised volume therapy is essential. However, when volume loading is not tolerated, such as in patients with pulmonary oedema, vasopressors should be considered despite the risk of renal vasoconstriction. The use of noradrenaline in donors does not have a negative effect on graft function in recipients. This is most because the harmful effect of a low blood pressure outweighs the potential renal vasoconstriction caused by vasopressors. On the basis of the current data, a clear recommendation for the use of vasopressors cannot be made; however, it seems sensible to avoid hypotensive episodes, especially after reperfusion.

Postoperative care
There are many aspects regarding the postoperative management of renal transplant patients. First, nephrotoxic agents should be avoided. Second, optimised volume therapy is essential, for example treatment based on the urine output. However, no recommendations or algorithms have yet been published or evaluated. Third, immunosuppressant medication has to be continued. Most patients receive triple immunosuppression consisting of calcineurin inhibitors, anti-proliferative agents and corticosteroids. Some patients, such as those receiving a living donor organ, may profit from an immunosuppression induction therapy with anti-thymocyte globulin administered after induction of anaesthesia. As antithymocyte globulin can induce an anaphylactic reaction, it should be given carefully over a period of 60 min. Because of the use of immunosuppressive therapy, sterile conditions for the placement of a central venous catheter are essential. Fourth, there are no recommendations as to whether all renal transplant patients should be admitted to the ICU, as their risk hospital-acquired infection is increased. When they are treated in the ICU, for example if they require mechanical lung ventilation, their outcome is worse compared with other patients.

Conclusion
Delayed graft failure and adverse cardiovascular events remain common complications after renal transplant surgery. An extensive preoperative ‘work-up’ is required to identify risk factors, to improve cardiac conditions, to treat hyperkalaemia and acid-base disturbances and to develop individualised and tailored perioperative therapy regime. This, in combination with optimal care for the living donor, the avoidance of potential nephrotoxic drugs, the implementation of goal-directed haemodynamic management and optimised postoperative care, may improve outcome after renal transplant surgery.

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